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TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION

MEETING HELD IN WASHINGTON, D.C., APRIL 30, MAY 1 and 2, 1928

(Continued)

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END RESULTS IN HODGKIN'S DISEASE AND LYMPHOSARCOMA TREATED BY THE MIXED TOXINS OF ERYSIPELAS AND BACILLUS PRODIGIOSUS, ALONE OR COMBINED WITH RADIATION.

By William B. Coley, M.D.

of New York

In 1915, in a paper on *Primary Neoplasms of the Lymphatic Glands including Hodgkin's Disease,*[1] I reported the end results in 167 cases treated almost entirely with toxins alone. Up to that time radiation had been used with but little success in these cases. While this method (radiation) has since become the generally accepted one in the treatment of lymphosarcoma and Hodgkin's disease, only very recently have the end results in a large series of cases been published. Among the most noteworthy of these publications are the report of Minot and Isaacs,[2] as well as that of Burnam[3] and of Stone.[4] From these data I believe it is now possible to get a fairly accurate estimate of the value of radiation in the treatment of lymphosarcoma and Hodgkin's disease.

It has been found that while radiation has resulted in a marked diminution in size—and in some cases, a complete disappearance—of the enlarged glands, in most cases the disease recurs after a longer or a shorter interval and proves fatal in practically every case. Just how much radiation adds to the duration of life of an individual suffering from lymphosarcoma or Hodgkin's disease is still problematical, at least, in the opinion of Minot and Isaacs. That this method of treatment has resulted in great temporary relief, there can be no doubt.

At the onset it is important to make clear what we mean by the term

[1] Coley: Trans. of American Surgical Association, 1915.

[2] Minot and Isaacs: Jour. Amer. Med. Ass'n, April 17 and 24, 1926, vol. lxxxiv, Nos. 16 and 17.

[3] Burnam: Jour. Amer. Med. Ass'n, October 30, 1926, vol. lxxxvii, No. 18.

[4] Stone: Canadian Practitioner, March, 1924.

"lymphosarcoma" or "Hodgkin's disease". For many years I have held that these two conditions, which are usually regarded as quite different and distinct, are actually quite closely allied etiologically, and bear such a close resemblance to one another that in some instances it is impossible to differentiate them either clinically or histologically. While on the one hand we may have a typical lymphosarcoma with definite clinical and histological features, and on the other, a typical Hodgkin's disease with discrete, freely movable glands, firmer in consistence than lymphosarcoma but not as hard as tuberculous or carcinomatous glands, and histologically containing the typical Dorothy Reed cells, we also have a great number of cases that are more or less atypical and fall between the clear-cut typical lymphosarcoma and the typical Hodgkin's disease. While it may be possible to regard these slightly different atypical conditions as distinct processes with definite etiology, I believe it is far more logical and more rational to regard them as varieties of a single disease. On this assumption we are justified in including them all in a general group, which is just what Minot and Isaacs have done, and to which group they have given the name *lymphoblastoma*.

In their publication referred to, Minot and Isaacs state as follows:

"The views and opinions concerning the nature and relationships of such cases are multiple, and thus students of the problem have utilized a constantly confusing terminology, and not infrequently disagree on the exact diagnosis of a given case. Some apply a term that is synonymous with one used by another, while at other times a special type of case is designated by a name used by others to cover a much broader group. Hodgkin's disease with the pathologic histology described by Dorothy Reed is sharply distinguished by many authorities from two other conditions that they term pseudoleukemia and lymphosarcoma. Others inappropriately include as Hodgkin's disease all, more often some, cases of the latter two conditions, and the terms malignant lymphoma and lymphadenoma have been used for such a group alone. Some contend that two types of lymphoblastoma may occur in one patient. Confusion in the group called lymphosarcoma arises because of differences of opinion as to what constitutes this condition and the lack of appreciation of the difference between the origin of tumors involving structures composed of much lymphatic tissue. Pseudoleukemia and aleukemic lymphocytic or lymphoblastic or lymphatic leukemia are essentially synonymous, as is at times the term aleukemic lymphadenosis. Chronic lymphatic leukemia with a leukemic blood picture is the form of lymphoblastoma most easily separated from others. However, except for the peripheral blood picture, no important distinction, even by pathological examination of tissue, can be made from cases termed pseudoleukemia or aleukemia, and the same case at different times may be given correctly the one name or the other."

While the systemic nature of Hodgkin's disease had been recognized by many writers, and this point fully established by Gowers [5] in his exhaustive paper published in 1879, in which he described the lesions as involving not only the lymph-nodes and spleen, but also the skin, intermuscular tissues, bones, brain, soft palate, pharynx, tonsils, esophagus, stomach, small intestine, large intestine, pancreas, peritoneum, thyroid, thymus, trachea, lungs, pleura, diaphragm, pericardium, heart muscle, suprarenals, kidneys, testes and ovaries, only recently has our attention been called to the fact that the disease involves not only the nervous system, but, as Ginsburg [6] has pointed out, the

[5] Gowers: System of Medicine, Philadelphia, 1879, vol. v, p. 306.

[6] Ginsburg: Archives of Internal Medicine, April, 1927, vol. xxxix, pp. 571–595.

skeletal bones as well. According to the latter, "the impression is still widely prevalent among physicians that the nervous system is so rarely involved in Hodgkin's disease as to be ignored in the differential diagnosis of diseases of the nervous system. Not only did I fail to see Hodgkin's disease mentioned in the standard textbooks on diseases of the nervous system, but even in the excellent recent monograph of Elsberg on *Tumors of the Spinal Cord*,[7] the condition is ignored completely." Ginsburg states that in a series of thirty-six patients with Hodgkin's disease observed at the Montefiore Hospital during the years 1914 to 1925, ten patients, or 27.7 per cent., showed invasion of the nervous system.

In the opinion of Ginsburg, the etiology of Hodgkin's disease still remains obscure, and a specific form of treatment has not been discovered.

In a paper on *The Relation of Hodgkin's Disease to Lymphosarcoma*, Gibbons of San Francisco,[8] discusses the nature of the process as follows:

"Two possibilities as to the nature of the process are apparent, *viz.*, is it a malignant, or is it an infectious process of the character of a granuloma? Most recent writers are inclined to the latter view. Reed is most insistent. Fischer, Clark,[9] and Simmons also hold this view. Longcope seconds it, though guardedly. Recent German publications also favor this view. Yamasaki,[10] regards the condition as a granuloma not of tuberculous but of unknown origin, which, however, may end in sarcoma. Wamecke,[11] although he has clearly recognized that lymphosarcoma cannot be separated from Hodgkin's disease, still adheres to this conception. From the study of my cases I incline strongly to the malignant theory."

Gibbons adds:

"It will be seen at once that many of these facts belong to malignant tumors as well as to infectious processes. We may have a rapidly growing sarcoma or we may have a slow one. We may have it accompanied by fever or we may not; and the fact that the fever of Hodgkin's disease is so variable in character, and sometimes not present at all, rather argues that it is not one produced by a definite infection. We see sarcomas which have existed for a long time, suddenly assume a very much accelerated growth. The mode of spread from diseased glands to adjacent ones is equally characteristic of malignant growths and of infectious diseases. The final stage of anæmia, cachexia, and disturbances of the body functions is very characteristic of the last stages of all malignant growths."

Regarding the nine cases which formed the basis of Gibbons' report, he states:

"Three of the cases were undoubtedly malignant, infiltrating and destroying surrounding structures as does any malignant growth. The only question that remains is, can these be classed with Hodgkin's disease, or are they different and to be classed as lymphosarcoma? Osler asserts that infiltration of the lung, as took place in one of my cases, does not occur in Hodgkin's disease, and that when such an infiltration does take place the disease is true lymphosarcoma. But in the light of the fact that this case, as well as the two other malignant tumors of the neck, present the same clinical features

[7] Elsberg: Tumors of the Spinal Cord, Paul B. Hoeber, New York, 1924.
[8] Gibbons: Amer. Journ. of the Medical Sciences, November, 1906.
[9] Clark: British Medical Journal, 1901, vol. ii, p. 701.
[10] Yamasaki: Zeitschr. f. Heilk., 1904, p. 269.
[11] Wamecke: Mitt. aus den Grenzgeb., 1905, vol. xiv, p. 275.

and the exact histological picture as the twenty-three cases so carefully studied by Reed, Longcope, and Simmons, and as the other six of my series, they must also be regarded as the same morbid condition. This being established, there would be no question as to the malignant character of Hodgkin's disease."

In conclusion Gibbons states:

"1. I agree with Reed, Longcope, and Simmons as to the histological picture presented by the tissues in Hodgkin's disease, but I do not agree that it is necessarily due to an inflammatory process.

"2. I assert that in most cases infiltration of the capsule of the diseased glands can be observed; in many cases an extension beyond the capsule occurs, and in some cases very evident infiltration of adjacent structures.

"3. The study leads me to believe that Hodgkin's disease is a process to be classified with malignant tumors."

One of the most important of recent contributions upon Hodgkin's disease is the Schorstein lecture of 1926 on *lymphadenoma*, (Hodgkin's lympho-granuloma), by Sir Humphrey Rolleston, (Regent Professor of Medicine, Cambridge University). It contains a brief note upon the history of the disease from its first definite description by Thomas Hodgkin and his first published series of cases in 1832; and Samuel Wilks in 1856 and 1865. A lucid discussion of the various theories on the nature and origin of Hodgkin's disease follows. Under the *Nature of Malignancy in Hodgkin's Lympho-granuloma"*, the arguments for and against regarding it as a neoplasm are presented in a most clear and judicial manner.

"That Hodgkin's lympho-granuloma is malignant in the sense that it leads to death is undoubted, and it differs from tuberculosis, which in many respects it closely resembles, in being constantly fatal and not becoming obsolete. . . . But further evidence suggesting malignant characters, such as invasion of adjacent bone and the histological characters of sarcoma, described years ago by Yamasaki and by Karsner, are now established, and Ewing considers this transformation into sarcoma ('Hodgkin's sarcoma') as a tumor *sui generis* and as by no means rare. He describes the new cells as endothelial in origin, but losing this character and appearing as large round cells, so that the term endothelioma is hardly applicable. Such a transformation as the result of long-continued irritation is, of course, well recognized, and Ewing has described it in lymphatic glands affected with chronic granulomatous infection. The occurrence of Hodgkin's sarcoma as a late result of Hodgkin's lympho-granuloma is rather remarkable, as it is very seldom recognized in the other infective granulomas.

"The development of sarcoma in Hodgkin's lympho-granuloma might be explained in one of two ways: (1) that some of the constituent cells of the lympho-granuloma proliferate so vigorously as to become a sarcoma, or (2) that the tissues surrounding a mass of lympho-granuloma are excited by the chronic irritation to a proliferation which eventually becomes sarcoma; this process Ewing compared with the occurrence of cutaneous squamous-celled carcinoma in the site of lupus.

"Prof. H. M. Turnbull, while fully recognizing the existence of the condition which Ewing terms Hodgkin's sarcoma, regards it as the 'lymphosarcomatoid' form of Hodgkin's lympho-granuloma and as inflammatory rather than neoplastic. Lymphosarcoma—the form of growth concerned in the malignant transformation of Hodgkin's disease—he considers as closely allied to it, and like it an inflammatory and not a neoplasm."

I agree with Professor Turnbull in so far as he attributes a common etiology to both Hodgkin's disease and lymphosarcoma, and I will go still

further in regarding them both as infectious processes. But this does not, in my opinion, make it necessary to exclude them from the class of neoplasms, since I believe that both sarcoma and carcinoma are likewise due to the irritation of some infectious agent.

As Rolleston well says, "Gye and Barnard's discovery of an ultra-microscopic virus and specific factor for new growths, and the existence of infective sarcomas make discussion of the *pros* and *cons* of the neoplastic nature of Hodgkin's lympho-granuloma rather an academic exercise than one of practical utility." This was written before later research work had failed to confirm the conclusions of Gye.

Rolleston's paper contains an admirable picture of the more important clinical manifestations of Hodgkin's disease.

Hodgkin's Disease of Bones.—It has long been recognized that the bone marrow was involved in certain cases of Hodgkin's disease. Ziegler [12] believes this occurs in 30–40 per cent. of cases, and Symmers [13] goes so far as to believe the bone marrow is affected in every case. It is only comparatively recently that clinicians have recognized the fact that in certain cases of Hodgkin's disease very definite metastatic tumors of the bone may be found. Symmers found definite bone invasion in 50 per cent of fourteen cases; and Sir Humphrey Rolleston believes that this invasion of bone by lymphadenoma (Hodgkin's disease), is now generally recognized. He states that "among thirty-nine necropsies of the London Hospital, Professor Turnbull found the bone marrow invaded in 49 per cent., the femur most often affected." From a study of the sites affected, he believes that the femur is invaded through the blood stream and the spine by direct extension from the affected retroperitoneal glands. Sir Humphrey Rolleston raises an interesting question whether all bone marrow infection is a part of a widespread reaction to the stimulus of an unknown virus, or whether it is secondary in the same way as a generalized tuberculosis is to an infection from a primary focus. Professor Turnbull concludes it is secondary.

After a careful study of my own cases with bone invasion, I am inclined to agree with Professor Turnbull's views. Here again we find a close analogy to malignant tumors and I believe that the bone invasion and the involvement of other glands and other tissues are closely allied to the metastatic tumors seen in cancer. In nearly all cases it starts in as a primary focus and the multiple tumors result from the infection carried through the blood stream.

Bone invasion may result in paraplegia. I have observed only one case of this kind and in this case the invasion of the spine was probably due to direct extension. The disease started in the glands of the right groin and iliac fossa and was controlled nearly a year by radium and toxins, then recurred and progressed rapidly in spite of further treatment. The lumbar glands were invaded and in a few months the patient developed paraplegia and died about three months later. The diagnosis was confirmed by Doctor

[12] Ziegler: Die Hodgkinsche Kranheit, Jena, G. Fischer, 1911.
[13] Symmers: Am. J. M. Sc., vol. clxvii, pp. 157 and 313, 1924.

Ewing from a microscopical study of the gland removed. I have had one other case with involvement of the lumbar vertebræ from Hodgkin's disease and here also the primary focus was in the inguinal glands.

I have had two other cases of direct invasion of the skeletal bones. One of these is of sufficient interest to warrant a brief citation.

The following personally observed case illustrates this tendency of the disease to metastasize in bones, and is interesting because of the remarkable effect produced by very large doses of toxins given after röntgen-ray had failed to control the disease.

CASE I.—M. G., female, aged forty-eight years. The patient's family history was negative. In October, 1916, she had noticed enlarged glands, the size of a marble, in both sides of the neck. These had gradually increased in size and number and were accompanied by a cough. In September, 1918, a tonsillectomy was performed by Doctor Blake, of Pittsburgh, Pa. Later on, a nodule was removed from the neck, and the pathologist of the Mercy Hospital in Baltimore, Md., pronounced it to be Hodgkin's disease. In February, 1921, the patient was referred to me by Dr. Lawrence Litchfield, of Pittsburgh. At this time she complained of pain, cough, inability to open mouth, and loss of weight and strength. For three years previously she had been treated with röntgen-ray. The disease had been held in almost complete control, but in the latter part of 1920, the glands of the neck became enlarged and masses appeared in both mastoids and frontal region. She was admitted to the Memorial Hospital on February 21, 1921, at which time physical examination showed a patient in fairly good general condition. There was a hard, fixed mass in the left frontal and parietal region, measuring one and one-half inches in diameter, and protruding one-half inch above the normal contour of the skull. In both mastoid regions were large, hard swellings, the size of an English walnut, firmly attached to the bone. In the right side of the neck below and posterior to the mastoid was a mass as big as an egg. Over the occiput was another swelling of the same character as the others. The jaws could be opened only about one-half inch. There was marked telengiectasis.

Increasingly large doses of the mixed toxins were given daily. After one week it was noticed that the masses in the skull were very much smaller, the patient was able to open her mouth wider, and she complained of less pain. By March 15, or after about three weeks' treatment, the pain had entirely disappeared, the masses were very much smaller, and her general condition was considerably improved. By April 26, the patient was practically symptom-free; there was no cough, no lumbar pain, her appetite was good, and the mobility of her jaws was practically normal. The patient was unable to remain in the hospital any longer, and the treatment was continued more or less irregularly and in smaller doses at home. After a few weeks she began to grow worse and in about six months she died.

The foregoing case, while not finally successful, is of the greatest interest for the reason that it is one of the few advanced cases of Hodgkin's disease with extensive bony tumor in both the mastoid and frontal bones. After a failure to control with röntgen-ray, the lesions practically all disappeared as a result of very large daily doses of toxins (25 minims a day—the largest dose I had ever given).

Whether the result would have been otherwise had I been able to keep her longer under treatment, it is impossible to say, but I believe that treatment was begun at a stage too far advanced to expect more than temporary control. If the systemic treatment with the toxins could produce such remarkable disappearance both of the tumor of the bone and soft parts in a few

weeks, it would seem sufficient evidence to justify our making use of this agent in the earlier stages of the disease when there is a greater hope of complete control.

Diagnosis of Hodgkin's Disease.—An entire paper might be devoted to the very difficult question of the differential diagnosis of lymphosarcoma and Hodgkin's disease from the other forms of glandular enlargement, *e.g.* tuberculosis of the glands, chronic or subacute lymphadenitis, or leukæmia but space will permit only a very brief outline of the more important features. The reader is again referred to the admirable paper of Sir Humphrey Rolleston for a lucid discussion of diagnosis and prognosis of Hodgkin's disease. What he has to say on the value and fallacies of biopsies is of especial interest:

> According to Rolleston, "*infiltration of the skin,* by Hodgkin's lympho-granuloma, apart from extension from immediately underlying lymphadenomatous glands, is much rarer than the skin changes of prurigo. In 1924 I could collect twelve cases only. It thus contrasts with mycosis fungoides, which, indeed, has been thought by Ranvier (1869) and K. Ziegler (1911) to be the cutaneous form of Hodgkin's disease, a view difficult to harmonize with the histological appearances. The cutaneous tumors in Hodgkin's lympho-granuloma may be small or large and flat; they grow slowly and seldom, as in Langley and Cole's cases, ulcerate. As a rule, the presence of the tumors has not been associated with pruritus. As they are usually part of the generalization of the disease, they are a late phenomenon in its course."
>
> In regard to "*Diagnosis from Sarcomatous Lymphomas*", Rolleston states: "The greatest difficulty is the clinical differentiation of Hodgkin's lympho-granuloma from lymphosarcoma and the closely allied malignant lymphocytoma composed of small lymphocytes, and from endothelial sarcoma. I have seen cases apparently running the clinical course of Hodgkin's lympho-granuloma show these histological appearances finally; the question arises whether, as probably most would consider, these conditions have existed from the start, or whether they have supervened as the result of Hodgkin's lympho-granuloma. Is there any evidence of this change, such as a biopsy early in the course of the disease showing the appearances of Hodgkin's disease, and later a necropsy proving the sarcomatous nature? It does not appear to me that the therapeutic test of X-ray exposures helps in distinguishing them."

The most important clinical signs of Hodgkin's disease are the following: An enlarged gland usually appears first on one side of the neck and is followed soon after by other glands on the same side; after a few weeks or months similar enlarged glands appear on the other side of the neck, and still later, in the axilla and groin. The spleen or liver, one or both, are not infrequently enlarged. The clinical features of the enlarged glands are often sufficiently characteristic to enable one to make a diagnosis of Hodgkin's disease. The glands are freely movable, discrete and very seldom fused as is so often seen in tuberculosis. They are firm in consistence but less hard than a carcinomatous gland and less soft than a lymphosarcoma. In a number of cases, especially after generalization has occurred, there may be an irregular temperature as high as 102° to 103° F. and lasting for weeks. There is nothing of diagnostic value in the blood examination. A severe and progressive anæmia is usually found in the later stages of the disease.

Prognosis of Hodgkin's Disease.—There is no evidence of a spontaneous cure ever having occurred and the universal fatality of the disease has long been recognized. The duration of life varies with the individual case, probably due to variations in the resisting power of the individual and to the variations of the infective agent. It is also very definitely modified by different methods of treatment. Life has been very definitely prolonged by drugs, *e.g.* arsenic, and by röntgen-rays, radium and toxins of erysipelas and Bacillus prodigiosus. In nearly all cases, except a very small percentage, the effect of treatment gradually diminishes and finally becomes nil and the disease goes on to a fatal issue. One case is recorded by Schniffner (quoted by Rolleston), that survived eleven years under röntgen-ray treatment. Some cases run a very acute course causing death within a few months or a year in spite of all treatment.

The following is an example of the difficulty associated with the early diagnosis of Hodgkin's disease especially with a type of Hodgkin's disease which progresses rapidly toward a fatal ending and which shows practically little or no effect from either radiation or toxins.

Case II.—Mrs. C. W., female, aged thirty-seven years, was referred to me by Dr. Donald Guthrie, of Sayre, Pa., with the following history: The patient had been in good health until February, 1925, when she noticed a small lump in her neck; there were no enlarged glands elsewhere. The gland in the neck was at first believed to be tubercular and was treated for several months with röntgen-ray. In August, 1925, a biopsy was performed by Doctor Guthrie, who regarded the condition as one of tuberculosis. In spite of further röntgen-ray treatment, the glands of the neck continued to increase in size, and on October 13, 1925, Doctor Guthrie performed a second operation. By this time it had become evident that the condition was Hodgkin's disease, in an advanced stage, with involvement of the right cervical region as well. The patient soon began to lose flesh and developed a cough. Röntgen-ray and fluoroscopic examination showed undoubted evidence of thoracic involvement.

When the patient came under my care in November, 1925, there was definite enlargement of the cervical glands on the right side of the neck and extensive involvement of the mediastinal glands, associated with marked dyspnœa. She was losing flesh rapidly. She was immediately started on treatment with the mixed toxins of erysipelas and Bacillus prodigiosus and in addition two radium-pack treatments (9000 mc. hours at 6 cm. distance) were given in December, 1925, and February, 1926. The treatment had practically little or no effect in checking the rapid advance of the disease; the dyspnœa became more and more pronounced, and after suffering intense agony for two weeks, the patient died on February 20, 1926. This was one of the most rapidly progressing cases of Hodgkin's disease that I have ever observed.

Burnam, of Baltimore, in a paper on *Hodgkin's Disease, The Journal, A. M. A.*, October 30, 1926, vol. lxxxvii, No. 18, reports the end results observed in a series of 183 cases of Hodgkin's disease treated at the Howard A. Kelly Hospital between October, 1913, and November, 1925. In his introduction, Burnam states that his original intention "to cover both Hodgkin's disease and lymphosarcoma was abandoned on account of the immensely greater material and the difficulty in analyzing it, and also from the fact that the two diseases are histologically and, in many ways, clinically quite distinct. The first is an infection, in all likelihood, and the second a

neoplasm. I believe that a large number of cases which have been treated and which showed the general distribution in the glands, the fever and the other clinical signs of Hodgkin's disease, may have been Hodgkin's disease. The tissue examinations, however, showed only a lymphoid hyperplasia and, as a consequence, these cases have been classified as pseudoleukæmia, or lymphosarcoma." The latter part of Burnam's statement would lead one to believe that the difficulty in differentiating Hodgkin's disease and lymphosarcoma was somewhat greater than he admits.

Burnam's series corroborates the repeated assertion that Hodgkin's disease is more prevalent in males than in females, his group including 118 males and 55 females.

The age incidence in this group of 173 cases was as follows:

	Per cent.
Up to 10 years	2.45
Between 10 and 20 years	15.33
Between 20 and 30 years	22.1
Between 30 and 40 years	22.3
Between 40 and 50 years	22.1
Between 50 and 60 years	10.4
Over 60 years	5.5

Burnam's series shows that in a great proportion of the cases the disease was apparently primary in the neck. He cites the place of primary gland enlargement as follows:

	Times	Per cent.
Neck	149	86.1
Mediastinum	13	7.5
Abdomen	11	6.1

I believe that a very large number of cases that have heretofore been classed as primary neck cases, should have been classed as primary mediastinum cases; and that failure to take early röntgenograms until after nodules had appeared in the neck has been responsible for the error.

Regarding the course of the disease, Burnam states as follows: "Very acute cases, especially of the intestinal type, last only a few weeks; chronic cases, extending over years, have been long recognized and generally regarded as rare. Two years is the period most authorities give for the average cases, and five years as the extreme limit." The average duration of life in 155 cases of Burnam's series was one year and five months.

In regard to treatment, Burnam believes that surgical removal does no harm in the early localized affections, easily and quickly removed; but extensive operative removals, entailing prolonged anæsthesia, and wide exposures, are unsound theoretically and in practice, and are apparently frequently followed by rapid extensions of the disease. The treatment employed in this series of 173 cases was, with few exceptions, radium alone. A number of the patients had had preliminary surgical removals, but all such showed evidence of disease at the time of treatment. Some had had röntgen-ray treat-

ment, and in some instances it was stated to have been without benefit. Burnam states, "I have recently been engaged in a comparative study of the two agents, radium and the röntgen-ray, and I am not able to state what the comparative ultimate results of the two methods will show. I do find that the reduction of glands, whether deep or superficial, is much more rapid from the radium than from deep röntgen-rays; furthermore, the effects are obtained with much less general upset to the patients. It seems that a very much smaller percentage of gamma rays is effectual than of röntgen-rays in producing similar results." Burnam points out that there are few conditions in which wider differences in susceptibility to radium are encountered than in Hodgkin's disease. He states, "It is obvious that a mass composed of fibrous sclerotic tissue will not reduce so rapidly as one made up almost entirely of cellular tissue and particularly of lymphocytes; but quite aside from differences due to architectural material, there are other and unknown factors, whether in the virulence of the infecting agent or in the defensive forces of the body, which produce striking differences in response to any fixed amount of irradiation. It is of paramount importance to begin with small doses and test out the results in each individual case. When the disease is localized, the dosage may, if it is necessary, be carried to several times that which is, on the average, effectual. In contrast, when the disease is widespread and when incomplete results are obtained by moderate dosage, it is best to go slowly and to recognize that palliation is an end desirable in itself."

The technic which Burnam recommends is "a uniform distance of two inches from the skin, a filter of one millimetre of copper and one millimetre of lead in all the superficial gland areas, and in the deep areas, unless cross-firing is feasible, a distance of from four to five inches. The dosage at the shorter distance is four gram hours, and at the greater from fifteen to twenty-five gram hours. This is about 50 per cent. of the erythema dose."

While Burnam believes that palliation is not to be discredited "and especially when it returns hopelessly ill people for months and even years to normal life, nevertheless I am convinced that certain cases of Hodgkin's disease are not only palliated but cured, from the clinical standpoint at least, and this is as far as one can go with any of the chronic infections, such as tuberculosis, or syphilis, or with any of the malignant new growths. Furthermore, while it is possible clinically to cure very widely spread disease, the percentage of relief is much smaller than when the disease is limited to its original site." Of this series of 173 cases reported by Burnam, 110 patients have died of the disease. Burnam has a group of twenty-eight patients whom he has classified as clinically cured, although two of them are dead, dying in the ninth year, in each instance from apoplexy. The average duration of life in this group was six years and three months.

The importance of beginning treatment as soon as possible after the disease has been recognized is shown by Burnam's end results. Of the entire series of 173 cases, only twenty-four were localized to a single region, and

of these fourteen are in the cured group of twenty-eight cases; twelve of these fourteen cases were cervical, one was mediastinal, and one was splenic. In the remaining 149 cases, only fourteen clinical cures were obtained, and none of these were in the very last stages, although six patients were very toxic and ill at the time treatment was undertaken.

W. S. Stone, of New York, in a report on two hundred cases of Hodgkin's disease treated by röntgen-ray and radium, at the Memorial Hospital, New York, states as follows:

In spite, however, of the extensive literature which has accumulated during the past twenty years, showing the undoubtedly favorable action of these agents, there is little discussion of the curability of Hodgkin's disease. There is also little in the literature to indicate the percentage of cases in which this mode of therapy is effective, the amount of palliation to be expected, and if actual prolongation of life has resulted. Such questions are especially difficult to answer because of the obscure nature of the disease, the location and multiplicity of its lesions and its varied course.

Regarding the permanent curability of Hodgkin's disease by these agents, our records indicate that palliation only can be expected. There are only five living without appreciable lesions or symptoms, one of whom has been well over four years. Three have remained well over three years, one only six months. One patient died after being well for over five years. It is of practical importance, according to the writer's experience, to accept its incurability as a fact in order to obtain the best palliative results. During our early experience a prompt and apparently complete regression of a chain of enlarged nodes led us, in the hope of producing a cure, to give prophylactic treatments over such areas, and also over areas where tumors might be expected to appear. Recurrent tumors, however, developed and new tumors appeared in the fields which had been treated prophylactically, applications to which were found to be less effective than when applied to areas which had not been previously treated. There also appears to be no other disease which requires, even for producing palliation, so many applications to so many areas, demanding, therefore, much consideration of the dosage, the choice of areas and the timing of the applications. The structure of the nodes, also, in Hodgkin's disease, is such that their reaction to these agents causes fibrosis and hardening of the tissues comparatively early, producing pressure upon nerves, blood vessels and neighboring organs, which may cause more distressing symptoms than originally existed. The deleterious effects of repeated and long-continued radiation are seen at autopsy upon these cases to the extent of widespread atrophy of the bone marrow. At present, therefore, we only apply the treatment to tumors as they appear, and often give more consideration to the possible effects upon normal tissues and the general condition of the patient than to the growth activity of the tumors in our timing of the applications.

Stone summarizes his views as follows:

1. X-ray and radium are only palliative agents in the treatment of Hodgkin's disease.
2. Palliation can be accomplished in 60 per cent. of cases, and complete restoration of health with or without complete regression of the tumors may result in about 32 per cent.
3. Restoration of health will often last for a year and rarely two, three or four years.
4. Palliation, if it is to follow, will begin after the first or second treatment.
5. Life may be prolonged one or two years.

DEJARDINS and FORD (J. A. M. A., September 15, 1923, p. 925) report the end results in 135 cases of Hodgkin's disease and fifty-five cases of lymphosarcoma observed at the Mayo Clinic between the years 1915 and 1920. In every case the diagnosis was verified by microscopical examination.

Concerning treatment, they state as follows: "The only form of treatment that

exercises noteworthy influence on such morbid states is irradiation by means of röntgen-ray or radium used either independently or in combination. . . . Even in the presence of extensive mediastinal glandular involvement, with or without pleural effusion, it is often possible for such adenopathy to disappear and the fluid to be absorbed. Unfortunately the improvement is not permanent; it may continue for a number of months or even two or three years, but sooner or later recurrences in the same or other places occur and are usually fatal." Evidently these authors were entirely unfamiliar with the results of treatment of Hodgkin's disease and lymphosarcoma by the mixed toxins of erysipelas and Bacillus prodigiosus reported at the American Surgical Association meeting in 1915.

Of the 135 cases of Hodgkin's disease reported by Dejardins and Ford the date of death was known in seventy-three cases. In these, the average duration of life was two years and seven months. In the fifty-five cases of lymphosarcoma, the average duration of life was found to be two years and three months. Of the entire series of Hodgkin's cases, seven (9.8 per cent.) were well for five years or more; and of the lymphosarcomas, six (11 per cent.) were well for five years.

In conclusion, Dejardins and Ford claim that while it is impossible to state that irradiation prolongs life, it is well known that in many cases it produces complete or partial control of the disease and adds greatly to the comfort and well-being of the patient.

In several instances these authors have noted a certain feature that I myself have observed in my experience with this type of disease, and that is, marked leucocytosis. In one of my cases of Hodgkin's disease, a blood test showed 83,000 white blood cells; and in one case of lymphosarcoma, there was found 247,000 white blood cells. While the latter case clinically resembled one of lymphatic leukæmia, microscopical examination showed it to be a lymphosarcoma.

The statistics of MINOT and ISAACS, already referred to, cover 232 cases admitted to the Massachusetts General Hospital between 1901 and 1925, 225 cases observed at the Collis P. Huntington Memorial Hospital, of Harvard University, between 1913 and September, 1925, and twenty cases seen in private practice since 1916, making a total of 447 cases. Seventy-six patients are living and 401 are known to be dead. Of this entire series, only seven patients were alive ten years or longer after the date of first observation. These seven were classified as follows:

1 female (age group 5–9)
2 males, 1 female (age group 40–44)
1 male in each of the age groups, 45–49, 50–54, 65–69
Total 7; 5 males, 2 females. Of these, 4 were irradiated and 3 were not.

Forty-one patients had lymphoblastoma for six years or more before death, of which 11 per cent. were treated by radiation, and 8 per cent. were not so treated. Of the 401 cases known to be dead, 238 were treated by radiation, and 163 were not irradiated. The latter group includes thirty-three patients who underwent a surgical operation with removal of a considerable amount of diseased tissue. According to Minot and Isaacs, "The patients treated by surgical measures, whether or not they received röntgen-rays or radon, had lymphoblastoma on the average 3.67 years, or 1.11 years longer than the average duration (2.56 years) of the disease in the 334 not undergoing a therapeutic operation. The chances of the former living beyond three years from the time of their first symptoms were greater than for the whole group of irradiated patients. However, the percentage dying a year or less after the onset of disease was the same as for the cases given no especial treatment, and only 10 per cent. less than for the latter group at the end of the two-year period."

The results of Burnam with radium are more favorable than any that have been obtained by other men. The fact that the majority of his series,

well five years, occurred in cases treated in the very early stages of the disease, emphasizes the great importance of early diagnosis and early treatment. It would seem to still further support the view of Professor Turnbull that the disease begins in a single focus and later is carried through the blood stream to other glands and soon becomes generalized. If we wait until this generalization has taken place, we can hope for little more than temporary control. If we can recognize the condition when the disease is limited to a single focus or to a few enlarged glands in a single region, then we are certain to control the disease for a much longer period of time and it is not impossible that we may effect a permanent cure.

This brings up the question of the value of surgery in Hodgkin's disease and lymphosarcoma. From my own experience I am of the opinion that an early biopsy is extremely important in most cases of enlarged glands, especially in young adults and especially when such enlargement cannot be easily accounted for by some adjacent focus of inflammation, *e.g.* in the throat or nasopharynx in the case of cervical glands. One must recognize frankly the fact, that it is extremely difficult to make a diagnosis from a small gland removed at biopsy between Hodgkin's disease or lymphosarcoma or simple hyperplasia. It has been my experience in three or more cases after having removed a gland from the neck in a case of suspected Hodgkin's disease or lymphosarcoma, to receive a microscopical report of chronic inflammation, no evidence of malignancy, and yet in each case the subsequent clinical history showed that it was a case of Hodgkin's disease or lymphosarcoma. In other words, in certain cases we shall still be in doubt after the biopsy report and in a case of negative report we must decide upon our diagnosis and treatment from the clinical evidence alone. Fortunately in the majority of cases of Hodgkin's disease or lymphosarcoma the pathologist will be able to make a positive report and this fact is what prevents us from losing faith in the biopsy and permits us to obtain most valuable help in the majority of cases.

If the biopsy gives positive evidence that the enlarged gland is Hodgkin's disease or lymphosarcoma, what is the best course to pursue? If it was a solitary gland and was completely removed in the biopsy, then it is my opinion that the patient should be put upon a course of röntgen-ray treatment and should receive systemic injections of toxins two or three times a week for a period of six months, in moderate doses that will interfere but little with his ordinary routine of life. If the gland was not solitary, but one of a few regional and well localized glands that apparently can be successfully removed by surgery, then I believe surgery should be performed, followed by prophylactic local treatment by radium and systemic toxins. In the more advanced cases in which several regions and glands are affected and especially if the röntgengram shows the mediastinum to be involved, I believe surgery should not be tried. It can do little good and may do much harm by still further generalizing the disease.

A study of my own cases in which surgery was employed would seem to support the foregoing views.

While I do not go so far as Bunting and Yates do [14] in believing that the disease is strictly local in its origin, at least when the patient first consults a physician or surgeon, and, therefore, should be treated by radical surgical operation, I do believe with Stone as well as Minot and Isaacs, that in a few very early cases when the disease is apparently confined to one or a few glands, and these regional, surgical removal followed by local radiation and prolonged systemic toxin treatment offers the greatest hope of controlling the disease. This group of cases, however, represents a very small percentage of the total.

Stone has pointed out the difficulty of the problem of adjusting the proper dose of radium to the individual case. No two cases are alike; and the dose that might be of great advantage to one patient might do great harm to another. In an advanced case with much fibrosis, radiation is of little value and may do positive harm, increasing the anæmia and lowering the general vitality. Minot and Isaacs and others have pointed out the dangers of too large doses of radiation in the acute highly cellular cases, and in a number of cases the evidence is very positive that radiation has hastened a generalization of the disease.

While I believe that radiation has proved of very great value in the treatment of both lymphosarcoma and Hodgkin's disease, the weight of opinion at present is that this method can be regarded as palliative only, and not curative, in the great majority of cases. It is true that Burnam's results show that in a considerable number of cases of Hodgkin's disease, radiation has kept the disease under control for a long period of time, sufficiently long to warrant classing the cases as cures. On the other hand, the statistics of Minot and Isaacs and of Stone, have not shown these lasting results either in lymphosarcoma or Hodgkin's disease. It is possible that Burnam's series covering, as it doubtless did, mostly private patients, may represent a higher percentage of cases in the early stages of the disease when radiation accomplishes much more than it does in the later stages. Furthermore, being private patients, they were under much better control, and treatment could be carried out much more satisfactorily than was possible in the series reported by Minot and Isaacs and by Stone representing almost entirely cases observed in the out-patient department. In view of these facts, we must admit that the present results in the treatment of lymphosarcoma and Hodgkin's disease are far from ideal; and I believe that the profession should welcome any aid that might be given to radiation, in the way of some systemic remedy or agent.

While this disease (or group of diseases) may be, and probably is, local at the beginning, it is nevertheless true that it is far from being local when its true nature is recognized and treatment is begun. In the majority of cases, instead of finding a solitary enlarged gland, we find a large number

[14] J. A. M. A., vol. lxiv, p. 1953, June 12, 1915.

of glands, and usually these are not confined to a single locality, like one side of the neck, but they involve the mediastinal, axillary, inguinal, and even the retroperitoneal or mesenteric glands as well. If this is true, it becomes apparent that the satisfactory treatment of all these glands, superficial and deep, by a local agent like radiation, becomes a very difficult and often impossible task. While radiation can accomplish much in the way of palliation in most cases, a cure or prolonged control of the disease is rarely obtained. In such cases I believe that systemic injections of the mixed toxins of erysipelas and Bacillus prodigiosus offer a very definite aid to local radiation of all the enlarged glands. That this opinion is based not merely upon theoretical considerations but upon actual results in a large number of cases treated before radiation was employed, has been shown in detail in my paper of 1915. Here we find that upward of 10 per cent. of the cases treated by toxins alone have recovered and have remained well from three to more than twenty years. This would seem to be ample ground for advocating a combination of toxins and radiation.

In his paper already referred to, Burnam has stated that he has used the toxins extensively in Hodgkin's disease and found them to be of no value. It would be interesting to have a more detailed report from Burnam stating in how many cases the toxins were used, in what type and in what stages of the disease, and especially, whether the toxins were used alone or in conjunction with radiation and how long the treatment was continued. If used with radium, it would be extremely difficult to estimate the relative value of either agent. Were my series confined to cases treated by a combination of toxins and radiation, no matter how successful the results were, I should hesitate to say just what part the toxins played in accomplishing these results. However, we have a large group of cases of lymphosarcoma and Hodgkin's disease in which the toxins were used alone and in which it is impossible to attribute the favorable results obtained to any other agent.

If it could be shown that it is possible to obtain equally good results with radiation, there might be some reason for not employing the toxin treatment in lymphosarcoma; but no one has thus far reported any results from radiation that equal the results obtained from toxin treatment, either in regard to the number of successes or the durability of the cures.

While all the successes with the toxins have been obtained by the use of interstitial or intramuscular injections, I believe that it might be possible to obtain far better results from intravenous injections. Some fifteen years ago I tried intravenous injections in two or three cases, but owing to the severe reactions that followed I feared that this method might prove too dangerous and therefore abandoned it. About two years ago, at the suggestion of my son, Dr. Bradley L. Coley, I began again to use the intravenous method and we have used it in a considerable number of cases since. While we have not had any fatalities, we are not yet ready to advocate it as a routine method for the reason that very severe reactions often follow a minute dose (one-twentieth minim). The susceptibility of the different individuals varies

greatly. In one case a dose of one-eighth minim injected intravenously was followed by a temperature of 104° or 105° F., while in another the temperature rose to 105.5° following an injection of one-twenty-fourth minim. I have had a temperature of 104° follow an initial dose of one-fortieth of a minim in an adult. The intravenous method should never be used until the susceptibility of the patient has been ascertained by the use of interstitial injections given over a period of at least one week. The initial dose given intravenously should never be more than one-twenty-fourth minim. A number of cases that have failed to respond to interstitial injections have shown marked benefit from intravenous injections; and I believe that the latter, if given with care, offer greater promise of success not only in lymphosarcoma and Hodgkin's disease but in all types of inoperable sarcoma.

REPORT OF CASES OF SPECIAL INTEREST

CASE III.—*Hodgkin's disease or lymphocytoma, treated with toxins, radium and röntgen-ray. Disease more or less under control for three and one-half years. Death from pneumonia; autopsy.* R. McC., male, aged fifty-two years, came under my care on July 10, 1921, with the following history: In the early part of 1920, while on a sea voyage, he first noticed a swelling under the chin; this lasted for three or four days. It is interesting to note that other members of his family were affected in the same manner. From that time on, the patient claimed that he had never really felt like himself again. In the beginning of 1921, general weakness, which previously had not been so marked, became striking; and he suffered from an attack of lumbago also. In April, 1921, the patient was shocked on noticing for the first time his extreme pallor; soon after this he experienced shortness of breath. On May 13, 1921, he came under the care of Sir Humphrey Rolleston, whose report of the case is as follows: "Patient when first seen had had dyspnœa for a month. Pale aspect at first suggestive of chronic renal disease but urine normal, and blood pressure 165 systolic, 80 diastolic. Enlarged discrete glands on right side of neck; enlarged irregular liver; doubtful mass about splenic flexure; no sore tongue. X-ray report does not suggest carcinoma of stomach or colon. Blood with low color index, otherwise suggests early pernicious anæmia or secondary metastases in bones. On May 30, after rest and arsenic, some improvement of blood and general feeling. July 27, after moderate business activity, worse; glands were enlarged; gland in right groin, also gland in left side of neck. *Röntgen-ray Examination.*—May 17, 1921; report as follows: 'Enlarged glands in root of right lung; heart enlarged.' *Blood Examination.*—May 13, red blood cells, 3,165,000; white blood cells, 4,400; hæmoglobin 57 per cent. May 28, 1921, red blood cells, 3,370,000; white blood cells, 5,000; hæmoglobin 55 per cent. June 27, 1921, red blood cells, 2,710,000; white blood cells, 4,800; hæmoglobin 43 per cent."

The patient came under my care on the day of his arrival from Europe on July 10, 1921. Physical examination at this time showed him to be very anæmic and cachectic, with evidence of marked dyspnœa on the slightest exertion. Enlarged glands, discrete and fairly firm in consistence, were found in the cervical and supraclavicular regions as well as in the axillæ and groin. The spleen was markedly enlarged, and the liver was enlarged to the extent of two finger-breadths below the border of the ribs. My clinical diagnosis was that of Hodgkin's disease, primarily in the mediastinum. Dr. Evan Evans and Dr. Karl M. Vogel, both of New York, who saw the patient in consultation with me, concurred in this diagnosis. I did not believe that he could live more than three or four weeks. Doctor Vogel made a blood examination at this time and reported as follows: Red blood cells 2,500,000; white blood cells 4,400; hæmoglobin 45 per cent. In counting 300 cells, two megaloblasts and eight normoblasts and four microblasts were seen. Abnormal white cells were not seen. The red cells showed considerable

variations in size, very slight poikilocytosis and slight polychromasia. Punctate basophilia was not observed. *Röntgen-ray examination* at this time showed a large tumor in the mediastinum.

The patient was admitted to the Memorial Hospital on July 29, 1921, and a massive dose of radium (9000 mc. hours at 6 cm. distance) was immediately applied over the mediastinum. Four days later another massive dose of radium was applied over the spleen. He showed very little reaction to radium. Röntgen-ray treatment was given over the glands of the neck, axillæ and groin. In addition, he was put upon systemic injections of the mixed toxins of erysipelas and Bacillus prodigiosus, the initial dose being one-quarter of a minim. He proved very susceptible to the toxins and was never able to take a larger dose than three minims.

A gland was removed shortly after the patient's admission to the Memorial Hospital, and submitted to Doctor Ewing for microscopic examination. His report is as follows: "Chronic lymphadenitis; no definite signs of Hodgkin's. The cellular overgrowth is considerable but not enough for lymphosarcoma which it resembles."

As the clinical evidence of Hodgkin's disease or lymphosarcoma was so strong, little attention was paid to the negative microscopical report based upon the examination of a small gland. Seven weeks after the patient's admission to the hospital examination showed changes to have taken place which were very remarkable: all the glands had disappeared, and the spleen and liver had returned to normal. The blood picture, however, was distinctly worse, radiation having caused a fall in the white blood cells to 1,000, and the red blood cells to 2,210,000; hæmoglobin 33 per cent. A blood transfusion was given and was followed promptly by marked improvement. During February, 1922, his hæmoglobin remained stationary, with moderate fluctuations, in the neighborhood of 80 per cent., and his white-cell count was normal. No radiation was given during this period. He received only moderate doses of toxins ranging from 1½ to 2 minims, which produced a slight reaction, temperature of 99.5, but no chill. In August, 1922, one moderate röntgen-ray (low voltage) treatment was given over the axillæ, neck and groin; and he received another transfusion on September 22, 1922.

Physical examination in November, 1922, showed distinct enlargement of the mediastinum. Röntgen-ray examination of the teeth revealed numerous abscesses about the roots, and two of the lower teeth were extracted. The effect of the last transfusion was very much less marked than that of the first, and was more temporary. He was becoming rapidly weaker, even sligh exertion causing dyspnœa; his hæmoglobin had gone down to 45 per cent., his red blood cells to 1,800,000, and his general appearance was very anæmic. No glands could be felt in the neck or axillæ; the inguinal glands were palpable, and enlarged glands could be felt in both iliac fossæ.

He was given another transfusion of blood (750 c.c.). Two days later another radium-pack treatment was given over the iliac fossa and groin. Between November 15 and November 23, four more teeth were extracted. On December 5, 1922, the patient went to Camden, South Carolina. During the next month he showed steady and rapid improvement; he was able to play eighteen holes of golf a day without fatigue. In May, 1923, slight enlargement of the glands was detected in the cervical and axillary regions as well as in the groin; the retroperitoneal glands also were slightly enlarged. In June, 1923, a radium-pack treatment (9,000 mc. hours) was given over the groin, and Röntgen-ray treatment to the other superficial glands; in addition, the toxin treatment was resumed. *Röntgen-ray examination* at this time failed to show any evidence of enlargement of the mediastinum.

During the next eighteen months the patient received a transfusion every four or five weeks by Doctors Coley (B.L.) and Patterson. At first 600 or 700 c.c. were given, but this amount was later increased to 1,000 c.c. (from two donors). The last transfusion was given on December 6, 1924. It was necessary for the patient to travel some two hundred miles, in mid-winter, to get this transfusion, and on the way he caught a slight cold; temperature of 100. He was kept in New York for one week until his

cold had apparently disappeared and his temperature had returned to normal; but on the way home he caught more cold, which developed into pneumonia and caused his death in two days.

An autopsy was performed by Dr. Stanley T. Fortuine and the tissues were examined by Doctor Ewing, whose report is as follows:

"In all the organs from which slides re-submitted (liver, spleen and lung) I find a malignant tumor of the type of malignant small-cell lymphocytoma.

"The spleen section shows a diffuse growth of small lymphocytes obliterating all the normal structures of the organ. In the liver the infiltrations are limited to diffuse lymphomas of the portal canals, while the lobules are free. The lung tissue shows a solid growth of lymphocytes filling the alveoli, but not destroying the framework of the lung.

"This type of tumor is a rather rare but well recognized type of lymphoma, generally called malignant lymphocytoma. It is nearly always systemic, affecting the whole lymphatic system and eventually the organs. It is related to lymphosarcoma and to pseudo-leukemia, but differs from the usual type of lymphosarcoma, in that the cells are small lymphocytes. It is one of the most malignant tumors known. Of the causation nothing is known. I believe all such cases are fatal, without regard to the method of treatment."

This case is of interest from the fact that it shows a far advanced malignant process involving the lymphatic glands to have been kept under partial control for a period of three and one-half years, the patient then dying of pneumonia. According to the autopsy, however, the disease was steadily progressing and, undoubtedly, would have caused death in a comparatively short time even if the patient had not contracted pneumonia. The case further illustrates the importance of paying little heed to a negative microscopical report based upon an examination of sections from a small gland.

CASE IV.—*Round-cell lymphosarcoma of neck and supraclavicular glands, recurrent and inoperable. Patient well twenty-five years after treatment.* A. P., female, aged two years and ten months. This patient was referred to me by Dr. E. J. McKnight, of Hartford, Connecticut, in March, 1902. A primary tumor had been removed by Doctor McKnight at the Hartford Hospital on January 27, 1902. No examination of the specimen was made, but the tumor rapidly recurred, and a second operation was performed in March, 1902. The specimen removed at this time was examined by Dr. W. B. Steiner, pathologist at the Hartford Hospital, who made a diagnosis of small-round-cell sarcoma. The tumor was considered too extensive for removal. The patient was first seen by me on March 8, 1902, at which time I found a series of tumors extending from the clavicle to the mastoid bone on the right side. The submaxillary and axillary glands on the right side were also involved. The clinical appearance of the disease was typically sarcomatous. I advised the toxin treatment, which was carried out by Doctor McKnight for about three months. There was immediate improvement followed by complete disappearance of the tumor.

This patient was shown before the Clinical Congress of Surgeons of North America on November 12, 1912, and at a clinical conference at the Memorial Hospital on November 7, 1918. A letter received from her in 1927 stated that she was married, had four children, and was in excellent health.

CASE V.—*Inoperable melanotic sarcoma of the neck which entirely disappeared under an accidental streptococcic infection. Five years later developed round-cell sarcoma of the cervical glands which was treated with toxins and radium. The disease entirely disappeared and the patient is in excellent health thirteen years after the appearance of the melanoma.* V. B., female, aged seven and one-half years. The patient had always been in good health until February, 1915, when a swelling of the left jaw was noticed. Two weeks later the right side of the neck began to swell and enlargement of the cervical glands was noticed. An examination was made by Dr. W. F. Mercer, of Richmond,

Virginia, who pronounced the throat, nose and ears normal. The patient was then examined by Dr. Robert C. Bryan, of Richmond, Virginia, who found the submaxillary, cervical and supraclavicular glands symmetrically enlarged and matted together. The enlargement was more pronounced on the left side. A provisional diagnosis of Hodgkin's disease was made. The blood examination was negative.

On July 7, 1915, Doctor Bryan made a small incision over the submaxillary gland at the angle of the left jaw and removed two small glands. These were examined microscopically by Dr. S. B. Moon, of the Medical College of Virginia, who made the following report:

"The sections are composed mainly of actively proliferating embryonal connective tissue cells, mainly spherical, but varying widely in shape and size. An occasional giant cell is seen. The vessel walls are thin or lacking, and when present, are intimately associated with the tumor cells. In some areas pigment granules, apparently melanin, are abundant in the cell protoplasm. Fibro-elastic tissue, fat, and striated muscle are definitely infiltrated by the tumor cells in their advance. *Diagnosis.*—Melanosarcoma."

The condition was quite inoperable, and a hopeless prognosis was made. The tumor slowly increased in size until December 25, 1915, when there was also beginning emaciation. On December 26 the neck became red and swollen and continued to increase rapidly in size. The patient's temperature rose to 106° F. and her pulse was 180. There was marked cyanosis, great dyspnœa and evidence of severe infection in the tumor. On December 27, the child became unconscious. On the following day, under primary anæsthesia, a median incision was made under the jaw and a large amount (from two to three ounces), of sero-pus was evacuated. A specimen was examined microscopically by Doctor Moon, who reported as follows: "Pus from neck is streptococcic with various saprophytes."

The infection slowly subsided but the wound remained open for several weeks. The tumors of the neck gradually decreased in size and in a short time entirely disappeared.

Doctor Ewing made a microscopical examination of the sections and confirmed the diagnosis of melanoma.

The patient later came to New York and was placed under my care for observation. She was presented before the New York Surgical Society on March 12, 1919.

In May, 1920, or five years after the appearance of the melanoma, she developed a rapidly-growing sarcoma involving the right cervical glands. A clinical diagnosis of round-cell sarcoma was made. I removed a portion of the tumor and submitted it to Doctor Ewing, who stated that it was a round-cell sarcoma with no pigment.

The toxin treatment was begun and kept up for four months. In addition, she received one radium treatment (2972 mc. hours in the form of a lead tray placed at 3 cm. distance). The tumors rapidly disappeared and the patient made a complete recovery. She was shown at a staff conference at the Memorial Hospital on January 28, 1926, at which time she was in excellent condition, eleven years since the disappearance of the melanoma and nearly six years after the disappearance of the round-cell sarcoma. At the present time, August, 1928, the patient remains in excellent health.

CASE VI.—*Large, inoperable lymphosarcoma of the small intestine treated with toxins and radium. Later metastases developed in the axilla. Patient in good health ten and one-half years later.* R. T., male, aged thirty-four years. The patient's father had died of cancer of the stomach. The patient had always been in good health until July 3, 1916, when he fell from a building, for a distance of eighteen feet striking on a cement floor; he landed in such a position that his upper abdomen received a sharp blow from his doubled-up elbow. Six or seven months later he began to feel pain in the upper left abdomen at the site of the injury. He consulted a number of physicians and surgeons in the State of Washington, who made the following different diagnoses: floating kidney, enlarged spleen, pancreas, sarcoma, tuberculosis of peritoneum, etc. The patient's own diagnosis was "internal cancer". In the middle of December, 1917, he came under the care of Dr. Charles H. Mayo, who made a clinical diagnosis of lymphosarcoma of the small intestine. Doctor Mayo performed an exploratory operation, by a left rectus

incision, revealing a large, inoperable tumor of the mesentery and small intestine. The tumor involved such a large segment of the mesentery that it was deemed unwise to attempt to remove it surgically and the wound was closed. The patient was then referred to me for toxin treatment.

Physical examination on January 7, 1918, showed a recent cicatrix, four inches long, over the left rectus muscle, the upper area of which was not entirely healed. Just underneath this incision was a solid tumor, about eight inches in diameter, deeply attached, but apparently connected with the mesentery or intestine. No enlarged glands could be felt. The patient's general condition was good; he had no pain nor any marked loss of weight. The blood test was negative.

The patient entered the Memorial Hospital and treatment with toxins and radium combined was begun at once. On January 8, 1918, he received his first radium-pack treatment consisting of 20,000 mc. hours applied at 10 cm. distance; on February 7, 1918, a second pack consisting of 16,000 mc. hours was applied at 10 cm. distance; and on March 3, 1918, he received 10,000 mc. hours at 7 cm. distance. He was made very ill by the radium.

On January 15, 1918, the toxin treatment was begun. It was given in small doses and increased very slowly, as the patient proved very susceptible and developed a high temperature, 103°, from a dose of two and one-half minims. After the first week's treatment, the tumor decreased about one-half in size and became much more mobile. The patient's condition steadily improved and he returned to his home on the West Coast, where the toxin treatment was resumed by his family physician.

On July 23, 1918, he again came to see me. Examination at this time showed on palpation, a very small, hardly perceptible mass at the site of the original tumor. As a precaution he was given two applications of radium (18,000 mc. hours at 7 cm. distance, each), and the toxin treatment was continued. During the year 1919 he received further applications of radium, totaling 44,283 mc. hours. The toxin treatment was kept up by his family physician, two or three injections a week being given, in doses not sufficiently large to interfere with his daily routine of life. I saw him again in May, 1920, at which time physical examination failed to reveal any definite mass in the abdomen; there were, however, two very small glands in both cervical regions. The lead tray, containing 3,000 mc. hours of radium, was applied at 3 cm. distance to each area; and the pack, (17,000 mc. hours), was applied over the abdomen. I next saw the patient on November 25, 1920, when he again had the pack, (6,344 mc. hours), applied over the abdomen. The toxin treatment was continued. He received no further radium until August 8, 1921, when the lead tray containing 2,870 mc. hours was applied to the left supraclavicular region, and the pack, (6,344 mc. hours), was applied to the abdomen. In January, 1922, a small nodule was noticed on the left elbow. This was treated with röntgen-rays and disappeared. In January, 1923, he received another pack treatment (18,026 mc. hours), over the abdomen.

The toxin treatment was kept up until November, 1923, after which the patient refused to take it any longer. About two months later, he noticed a slight enlargement of the glands of the left axilla, which steadily increased in size. I again saw the patient on January 20, 1925, at which time physical examination showed enlargement at the site of the old intraabdominal tumor, with apparent involvement of the retroperitoneal glands; the cervical and inguinal glands were normal. In the left axilla was a mass about the size of a large goose egg or a small orange, soft in consistence, movable and extending from some distance beneath the edge of the pectoral muscle. The radium pack was applied as follows: On January 22, 1925, he received 12,000 mc. hours over the abdomen at a distance of 10 cm.; on January 24, he received 10,000 mc. hours over the left pectoral region, at a distance of 10 cm.; and on January 26, he received 10,000 mc. hours over the left axilla, at a distance of 6 cm.

On February 4, 1925, he entered the Hospital for the Ruptured and Crippled, where I removed the tumor of the axilla surgically. Microscopical examination proved it to be a typical lymphosarcoma.

This case is of interest for the following reasons: first, it shows that a rapidly growing lymphosarcoma of the small intestine has been almost completely controlled for a period of ten years, the patient remaining in good health during most of the period; second, it shows that even when metastases have developed, one should not abandon treatment. In this case, the metastatic tumor in the cervical glands completely disappeared under further treatment. The latest and most extensive metastasis in the axilla did not occur until November, 1923, some time after the toxin treatment had been discontinued. While in all probability the disease will prove fatal in the end, I believe there is a reasonable hope of keeping it under control for some considerable time to come. I do not believe this result could have been obtained by toxins alone or radium alone, but was due to the combined treatment with both agents.

CASE VII.—*Lymphosarcoma of neck, or Hodgkin's disease, treated with toxins. Patient well twelve years later, when she died of another trouble.* S. K., female, aged fifty-five years, was referred to me in December, 1913, by Dr. Arpad G. Gerster, with the following history: A tumor had been removed from the right side of her neck at Gouverneur Hospital nine years before. In March, 1913, a second operation was performed by Doctor Erdman for a local recurrence; the tumor removed weighed three-fourths pound and was pronounced lymphosarcoma by the pathologist of Bellevue Hospital. The tumor again recurred in the fall of 1913 and the patient was then referred to me by Doctor Gerster as an inoperable case.

Physical examination at this time (December, 1913) showed several tumors occupying the right cervical region between the mastoid and clavicle, varying in size from a hickory nut to a hen's egg. The tumors were smooth in outline, freely movable, more or less discrete; skin not adherent; consistence only moderately firm; no glands in either axilla or groin. No enlargement of the spleen or liver. The patient was put upon the mixed toxins of erysipelas and Bacillus prodigiosus. She proved very susceptible, the highest dose given being 5 minims. After fifteen treatments, the tumors had diminished markedly in size and became more freely movable, so that I believed it wise to attempt their removal by operation. This was done by my associate, Dr. William A. Downes, on January 15, 1914. Doctor Ewing's report on the specimen, dated January 15, 1914, reads: "Typical Hodgkin's disease; granuloma; giant cells; hyaline and fibrin areas."

The disease recurred shortly after the operation and grew more rapidly than before. She was then put upon röntgen-ray treatment, under which there was marked diminution in the size of the tumor.

After her discharge from the hospital I lost track of the patient and believed she had died. Eight years later I was called in consultation to see her and found her suffering from an acute abdominal trouble (probably gall-bladder). She was removed to the Memorial Hospital, but her condition was too advanced for operation and she died in a few days. There was no evidence of any return of the Hodgkin's disease.

CASE VIII.—*Far advanced Hodgkin's disease; diagnosis confirmed by microscopical examination; disappearance of lesions under toxins and radium. Patient well four and one-half years.* F. A. T., male, aged fifty-seven years. The patient's family history was negative. He had always been in good health with the exception of an attack of typhoid fever thirty-two years previously. His present illness started with a cough in the summer of 1921; for the next seven or eight months he felt very tired and weak. At the end of this time he noticed a lump in the left side of his neck. A diagnosis was not made until March 1, 1922, when a gland was removed and examined by the pathologist of the Buffalo Hospital for Malignant Disease, who pronounced it Hodgkin's disease. In the early part of March, 1922, he received röntgen-ray treatment of his neck. Shortly

afterward the glands in the right side of the neck and supraclavicular region began to enlarge. There was steady increase in size and the patient became weaker. Under further radiation the glands regressed somewhat. He was referred to me by Dr. R. P. Huyck, of Herkimer, New York, and was admitted to the Memorial Hospital on April 24, 1922.

Physical examination at this time showed a well-developed but poorly nourished male. The cervical, axillary and inguinal glands were all enlarged, firm in consistence, discrete and movable. There was a mass of glands on the right side of the neck, the largest just above the clavicle measuring one inch in diameter. The skin was not involved. On the left side of the neck was a similar gland just under the scar. The liver was palpable; and the spleen just palpable.

Röntgen-ray examination by Doctor Herendeen, April 24, 1922: "Plate of chest reveals a diffuse haziness through the right side with some infiltration in the right hilum."

On April 26, 1922, the radium pack (12,750 mc. hours) was applied over the mediastinum, at a distance of 10 cm. In addition, from May 4, 1922, to May 9, 1922, the patient received four exposures (fifteen minutes each) of röntgen-ray to the axillæ and groin. At the same time, treatment with the mixed toxins was begun and continued in gradually increasing doses during his three weeks' stay at the hospital. This was continued at home by his family physician, Doctor Huyck. A few weeks after his discharge from the hospital his general condition became very weak, in appearance he was almost cachectic, and he was strongly opposed to any further treatment. I saw him again and finally persuaded him to go on with the toxin treatment. This was kept up for six months. In early June, 1922, he began to show some evidence of improvement in his condition; this continued until at the end of two months all trace of the disease had disappeared, he had regained his normal health and was able to return to his work. I saw him from time to time and found him in excellent condition. Physical examination in May, 1926, showed apparently no evidence of the disease.

In June, 1926, he developed a tumor in the left hypochondriac region which was regarded by several surgeons, who were not acquainted with the patient's early history, as a tumor of the kidney. This was, undoubtedly, a tumor of the spleen. It increased rapidly in size, his general health began to deteriorate, and in spite of further treatment, he died on August 1, 1926.

In this case I think it is fair to assume that the treatment added four years to the life of the patient, who was in an advanced stage of the disease when the treatment was begun.

My later series of cases personally observed since 1915 includes fifty-eight cases of lymphosarcoma and thirty-nine cases of Hodgkin's disease. In the former group there were thirty-five males and twenty-three females, and in the latter twenty-two males and seventeen females.

Age incidence:

	Lymphosarcoma Cases	*Hodgkin's Disease Cases*
From 1 to 10 years	2	3
From 11 to 20 years	9	1
From 21 to 30 years	11	9
From 31 to 40 years	7	9
From 41 to 50 years	18	4
From 51 to 60 years	4	6
From 61 to 70 years	3	3
Not stated	4	4
	58	39

Locality in present series:

	Lymphosarcoma Cases		*Hodgkin's Disease Cases*
Neck	24	Neck	3
Retroperitoneal region	7	Groin	3
Axilla	3	Neck, axilla and groin	27
Groin	4	Supraclavicular region	1
Mediastinum	2	Cervical region	1
Tonsil	1	Mediastinum	1
Nasopharynx	2	Spleen	1
Multiple	15	Submaxillary region	1
		Multiple	1

Duration of symptoms in present series:

	Lymphosarcoma Cases	*Hodgkin's Disease Cases*
Less than 1 month	3	–
5 weeks to 3 months	7	5
3 to 6 months	13	6
6 months to 1 year	11	12
1 – 2 years	12	4
2 – 3 years	6	4
3 – 4 years	1	2
4 – 5 years	2	2
6 – 7 years	1	–
8 years	–	1
9 years	1	–
Not stated	1	3

An analysis of the cases that have remained well for five to twenty-two years may be of some interest (four others were well for three to five years). Of this group, fifteen were treated with toxins alone and three with toxins and röntgen-ray. This does not include a case of Hodgkin's disease that was treated with toxins alone by Dr. Charles E. Preston, of Ottawa, Canada, my old house surgeon; this case, which was well when last traced, twelve years later, might well be included here, as the treatment was carried out under my direction.

Site of Primary Tumor in Cases of Apparent Cure.

	Cases
Glands of neck	10
Tonsil and neck	2
Axilla	4
Mediastinum	1
Groin	1
Mesentery and small intestine	1
	19

The diagnosis was confirmed microscopically in all these cases with the exception of one, a very large tumor of the mediastinum which disappeared under toxins and röntgen-ray and had not recurred five years later when the patient was last seen.

One case was included in my earlier paper, in which, while not strictly speaking, a lymphosarcoma, was, apparently, a primary malignant tumor of the lymphatic glands.

This patient, the wife of a physician in Louisville, Kentucky, was referred to me in December, 1914, with an inoperable, four-times recurrent tumor that involved the cervical glands on both sides. While a microscopical diagnosis of melanotic sarcoma had already been made, I removed a gland for further study, and it was pronounced a malignant melanoma by Dr. James Ewing. I regarded the prognosis as quite hopeless but decided to give the patient a trial of toxin treatment. The injections were continued for nearly a year at home by her husband. Under this, and no other treatment, she made a complete and uninterrupted recovery. She remained well for more than nine years and then died of an independent trouble.

Of the thirty-nine cases of Hodgkin's disease included in my later series, only three remained well for a period of more than three years, and one of these died of the disease four years after the treatment was begun. Of the fifty-eight cases of lymphosarcoma, six remained well for a period of from three to ten years; two of these died a little over three years later, and the patient who has lived for ten years has marked evidence of the disease and is not expected to live much longer. One other case, No. VII (reported in my earlier paper, at which time the end result was not known) remained well for eight years and then died of another trouble.

A comparison of the results obtained in the later series with those of the earlier series will show the latter—in which treatment for the most part consisted of surgery and toxins—to be considerably better than those of the more recent series, in which treatment consisted of toxins and radiation. I think that the less favorable results obtained in the later series may be accounted for by the fact that most of these patients at the time of first observation were in a much later stage of the disease, the latter having become widely generalized in most cases, and most having been previously treated by radiation.

CONCLUSIONS

1. Lymphosarcoma and Hodgkin's disease should no longer be regarded as absolutely hopeless from any method of treatment.
2. These tumors are as a rule extremely radio-sensitive and are likewise responsive in a remarkable way to treatment with the mixed toxins of erysipelas and Bacillus prodigiosus.
3. It would seem logical to use the combined treatment, thereby securing the advantage of the local effect of radiation (radium or röntgen-ray) and the systemic effect of the toxins which have the power to reach hidden and remote glands beyond the reach of radiation.
4. These patients should be kept under the closest observation for a long period of time; and treatment should be kept up periodically for a number of years, especially in those cases in which the disease was generalized when treatment was begun.
5. Cases of lymphosarcoma so treated should show a cure or at least a

complete control of the disease for a long period (five years or more) in a very considerable number of cases, *i.e.* 10 to 15 per cent.

6. Typical cases of Hodgkin's disease still show a very bad prognosis; and permanent control can be expected in only a very small number of cases.

DISCUSSION: DR. HOWARD LILIENTHAL, New York City, remarked that in the treatment of lymphosarcoma and other forms of sarcoma he had found Coley's fluid to be of especial value in lymphosarcoma. Cases that he had had, for instance, had gotten well with Coley's treatment alone, with recurrence years afterward, and then a second cure by Coley's fluid with eventual apparent permanent cure.

He called attention to the fact that Coley has antedated Blair Bell in giving to the profession something which acts, as we may say, constitutionally instead of locally, as X-ray and radium do. Two years ago a young woman with Hodgkin's disease came to him with an enormous tumor of the mediastinum, which was proven to be Hodgkin's disease by the removal of a lymph-node from the neck. She was suffering from the usual symptoms of intense mediastinal pressure, the dyspnœa, the suffusion of the face and enlarged veins of the head and upper part of the thorax. He advised treatment by X-ray, although she had been given up entirely by the physicians at the Memorial Hospital in New York and had been sent home to die. Nevertheless, under X-ray treatment alone, there was in an astonishingly few weeks a complete disappearance of the symptoms of thoracic malignant disease, so that the chest appeared normal by X-ray and on physical examination. Now, after two years, she remains apparently perfectly well.

DR. CHARLES N. DOWD, New York City, said that he had seen a good many cases of Hodgkin's disease. He had not seen so many of lymphosarcoma of the neck. They usually had come to him with tremendously distended necks. Among these cases he had two who have now lived, one as nearly as he could remember about fourteen years, and the other about ten years.

The surgical operation—which, after all, is not very difficult, because Hodgkin's-nodes come out very easily—has been repeated on one case three times, and there has been very good radiation carried on. The other case was treated also by radiation and by surgery. The fact that he had two of those cases alive after this long period and the fact, as Doctor Coley tells us, that cases who have been treated by surgery have a longer expectation of life than those who have not, would lead him to believe that surgeons ought to endeavor to give these patients the advantage of surgical operation at an early stage in the disease.

The enlargement usually begins in a small group of lymph-nodes on one side of the neck. When one can get hold of them in fairly early stage, one may well believe that surgery offers more than has generally been supposed.

If the palpable nodules are removed and then the locus subjected to such further treatment as seems wise, we are doing the best for our patients.

Dr. Leonard Freeman, Denver, Col., mentioned the case of a man with bleeding from the stomach, pain after eating, loss of flesh, and general disability, upon whom he operated and found two apparently distinct conditions. One was an indurated ulcer near the pylorus and the other an extensive involvement of the distal one-third of the stomach and first part of the duodenum, with a soft, whitish, uniform thickening. There was also enlargement of the glands above and below the stomach, and around the pylorus and aorta—soft, yellowish-white glands as large as the last joint of a thumb.

It did not appear that a resection of the stomach would be of any value as regards cure, but it seemed necessary to relieve him from his symptoms; so the entire pyloric end of the greatly thickened stomach was removed, it being necessary to go directly through the growth, both on the duodenum and the body of the stomach itself. After the operation was done, the recovery was uninterrupted. A pathologic examination of the specimen showed it to be a lymphosarcoma; examination being made not only by the Denver pathologists, but a specimen being sent to Doctor Mills, at the Mayo Clinic, and also to the Columbia University, in New York, and pronounced lymphosarcoma in all instances. The patient was then put upon Coley's toxins and the deep X-ray, but carried out the treatment for a short time only, regarding it as unnecessary owing to his rapid improvement. At the present time he is apparently perfectly well. He has no stomach symptoms whatever thirteen months after he was operated upon. He is virtually normal except that his weight is somewhat less than it was, and there are some enlarged glands in his neck and groins which have decreased in size and seem as though they were about to disappear.

In spite of the diagnosis of lymphosarcoma made by the various pathologists, the question of Hodgkin's disease must be considered, especially in the light of the close connection of the two affections so strongly emphasized by Doctor Coley.

Dr. William B. Coley (in closing) remarked that if one could get early cases of single isolated glands, of the type in which Burnam had most of his successes, and, after removing the glands by surgical operation, give the patient a course of prophylactic toxin treatment, alone or combined with radiation, that a larger percentage of cures will be obtained.

He remembered a case that Dr. Charles H. Peck referred to him some fifteen years ago. Doctor Peck had operated upon a large tumor in the region of the submaxillary gland, performing what he regarded as an incomplete operation, and then turned the patient over to Doctor Coley for toxin treatment. The gland removed was examined by the pathologist of the Roosevelt Hospital and pronounced to be a lymphosarcoma. On reviewing the section later on, after the patient had recovered, the pathologist stated that he was in doubt as to whether it was a lymphosarcoma or Hodgkin's disease. The slide was mailed to Doctor Welch, but, unfortunately, was lost in transit. At

any rate, the patient was alive and well twelve years later; and it does not matter very much which of the two diagnoses was correct.

He had another case, a girl aged eight years, with a glandular tumor of the neck believed to be lymphosarcoma. It was impossible to perform a complete operation, but a portion of the tumor was removed and submitted to Doctor Ewing, who pronounced it to be a round-cell sarcoma. One single dose of radium was given, supplemented by toxin treatment for several months. This patient is alive and well over eight years later. A full history of the case will be found in the text of Doctor Coley's paper.

It is very important to make a diagnosis early, and not wait until the end result has determined the nature of the condition. In order to make an early diagnosis, a gland should be removed at once and examined microscopically.

One of his most remarkable cases of lymphosarcoma of the neck occurred in a child aged two and one-half years. The whole side of the neck was involved, and the condition was pronounced inoperable by Dr. Walter R. Steiner, of Hartford, one of the leading pathologists of Connecticut. Under toxin treatment alone the patient made a complete recovery and is well at the present time, twenty-six years later.

The first illustration of the beneficial effects of the toxins in Hodgkin's disease occurred at the Memorial Hospital some eighteen years ago. The patient had all the clinical earmarks of Hodgkin's disease: markedly enlarged glands of the neck, cervical and axillary regions and groin, with enlargement of the spleen and liver, accompanied by a persistent fever, temperature of 102–03°. In this case he removed one of the glands, which was examined microscopically by Doctor Ewing, and pronounced a typical Hodgkin's (which was the clinical diagnosis of Dr. W. K. Draper). Under six weeks' toxin treatment all the glandular tumors disappeared, the spleen and liver returned to normal size, and the patient gained twenty-six pounds in weight; in fact, he felt so well that he refused further treatment and returned to work. Within less than a year the disease recurred. The patient would not consent to further treatment and died about six months later. If the toxins alone can accomplish what they apparently did in this case, in which there was no doubt of the correctness of the diagnosis, why should they not be employed as a systemic agent in practically all cases of Hodgkin's disease?

HÆMANGIOMA OF CHEST WALL

By Henry H. M. Lyle, M.D.
of New York, N. Y.

Case Report.—A woman aged twenty, was admitted to the Surgical Service of St. Luke's Hospital, New York, October 25, 1927, with the following history:

Three years ago without known cause a soft painless swelling suddenly appeared in the second right intercostal space close to the sternum. At first this swelling was only noticed when she bent forward or on standing erect; on lying down it disappeared completely. During the last year and a half the swelling has been growing larger and does not now completely disappear on lying down. In addition a small hard nodule has appeared in the swelling. The nodule is tender and at times cannot be found, at other times when caught it will suddenly slip from between the fingers and disappear. The patient noticed that when the nodule is absent the swelling is larger.

Examination revealed in the second right intercostal space two fingers breadth from the edge of the sternum a soft lens-shaped swelling, 3 by 2½ inches, with indefinitely defined borders. It is attached to the deeper parts, the skin is freely movable over it and there are no signs of discoloration or surface heat. Pressure does not influence the size of the mass but posture does. In the erect or prone position the swelling is diminished, on bending forward the tumor quickly resumes its usual size. When the mass is shrunken a hard round body about one-eighth inch in diameter can be felt; the nodule is suggestive of a bony or cartilaginous fragment. At times it slips from the fingers and seems to disappear between the ribs. Coughing slightly enlarges the swelling, it does not pulsate, no thrill is felt and no murmurs are heard. The mass gives the impression of being a cold or a latent bone abscess which connects with the thoracic cavity. The X-ray studies show an indefinite shadow three by four inches apparently in or just behind the anterior thoracic wall. The nature of the shadow was cleared up at operation. Plates taken after the operation failed to reveal it.

The patient was shown before the Surgical Conference and various diagnoses were made. The majority favored a cold abscess communicating with the thoracic cavity, a lipoma or a dermoid cyst communicating with the chest cavity.

At the operation a shirt-stud hæmangioma was found, the superficial lens-shaped expansion lay just beneath the pectoral fascia, the deep expansion lay between the pectoralis major and the intercostal muscles. The stem of the collar-button connecting the deep and superficial portions was composed of a dilated varix which contained a hard ivory-like phlebolith. The deep portion of the hæmangioma communicated by several branches with the vessels of the thoracic cavity. The phlebolith which was situated in the stem of the collar-button moved forward and backward like a ball-valve. When the patient sat erect it slipped backward and blocked the main communicating vessels, the same check-valve effect was produced when the patient lay on her back. On bending forward the phlebolith slipped into a side expansion and allowed a reflux of blood from the posterior to the anterior expansion. The operation was performed under local anæsthesia and the mechanism of the filling and the action of the phlebolith could be readily observed. The hæmangioma was excised *en masse* and its communicating branches to the thoracic cavity ligated. There have been no signs of recurrence and the patient has worked steadily since the operation.

DIVISION OF THE VAGI FOR PYLOROSPASM

By Charles H. Mayo, M. D.
of Rochester, Minn.

It is nearly fifty years since Billroth directed the attention of the medical world to the possibility of relieving, by surgery, obstruction of the pylorus due to gross ulcer. The preantiseptic period with its attendant mortality was marked by many changes in technic and methods. These changes became fewer with the advent of antiseptic and later aseptic surgery. Greater effort was made and greater success was attained in relieving symptoms and in curing ulcer than in finding the cause of ulcer. Such ulcers were called "peptic", a term which was self-explanatory as indicating the theory that they were caused by the local action of pepsin activated by acid but probably starting at the site of a few dead mucous cells.

Recently several methods of producing gross ulcers of the stomach and duodenum experimentally have been successful. One of these is that reported by Rosenow, who has produced hemorrhagic patches and erosions by injecting intravenously into animals bacteria that have been cultivated from excised ulcers of the stomach and duodenum of human beings. The bacteria show a fairly definite selectivity in their localization. There is a strong tendency, however, for such lesions to heal rapidly perhaps because the experimental animals are, of course, not subject to any factors for the development of ulcers other than the injected bacteria. The ulcers do not heal so readily if the general health of the animal is broken by the production of local foci of infection. This may be accomplished by infecting the teeth and thus developing periapical infections and excavations in the bone. Such local foci continue to feed bacteria into the circulation after the ulcer has been created by the intravenous inoculation.

Another method has been developed by Mann, who has caused ulcers to form with great certainty from mechanical deflection of the digestive fluids of both stomach and duodenum, by short-circuiting through an anastomosis of the duodenum into the ileum thus preventing all secretions poured into duodenum from passing through the jejunum. By dividing the pylorus and uniting the stomach to the upper end of the jejunum thus allowing all of the contents of the stomach to pass into the jejunum. Mann has succeeded in producing ulcers, a large proportion of which are formed just distal to the suture line of the gastrojejunal anastomosis.

From these experiments it would seem that there are undoubtedly several factors connected with the development of gastric ulcers. We must remember, however, that mechanical injuries of the stomach and bowel usually heal

rapidly without ulceration. It would seem, therefore, that there must be some other factor in the maintenance of chronic gastric ulcers.

Any large series of necropsies on the bodies of adults who have died from any cause shows that it is not uncommon to find the evidence of healed ulcers in the duodenum or in the stomach. These ulcers appear to have been healed for long periods. In many of these cases a history suggestive of gastric or duodenal ulcer, may not have been elicited and the relatives of the deceased are not able to recall any symptoms suggesting ulcers which the deceased may have complained of during life. It is highly probable, therefore, that many people have hyposensitive areas in the stomach while others have hypersensitive areas. Some patients who have ulcers in these areas complain very little and others very much. It has often been noted also that patients who have suffered repeatedly from attacks of ulcers of the stomach and duodenum and have been operated on two months or so after the last attack has ceased, are found to have open ulcers which from their appearance would lead one to believe that they should be causing pain. But they are not really producing pain any more than are the old so-called varicose trophic ulcers on the lower half of the leg which may have been open for weeks, months, or years. Trophic ulcers on the ball of the foot or on the heel also may be painless. Such ulcers, however, from time to time may become exceedingly painful. At such a time a little red spot is noted on one side of the circumference of the ulcer. This very slight marginal extension may cause great pain and disability lasting at least two weeks.

It would appear then, that, except in the presence of a deranged nervous (trophic) influence, both incisions and ulcerations in the body should heal. Is it not possible, that in the stomach the influence of the vagi in the chronicity of gastric ulcers has been overlooked? It is to stimulate observation in this direction that I am presenting this brief study.

Excellent studies by M'Crea and Brandt have shown that the pylorus and duodenum get their nerve supply from a large branch of the vagus that goes directly from the region of the cardia to the liver.

There is apparently some association between chronic appendicitis, diseases of the gall-bladder and ulcers of the duodenum and stomach. Just how it is brought about is not known, but when any one of these three structures is suspected of disease all three should be examined, especially in adults.

It is quite probable that the appendix comes first in the development of symptoms during contraction and spasm of the circular fibres, in a structure in which the wall is as thick as the rest of the bowel but with a very small lumen. The secondary influence may be on the outlet of the common duct, spasm of which may enormously reduce the amount of bile passing into the duodenum, thus causing excess of filtration by the gall-bladder. The influence of both appendicitis and gall-bladder disease on the pylorus is to produce pyloric spasm and it is probable that neither duodenal nor gastric ulcer occurs except when it is accompanied by pyloric spasm. May not, perhaps, the pyloric spasm precede the ulcer?

DIVISION OF THE VAGI FOR PYLOROSPASM

For the last two years in several cases in which it was evident that the trouble in the stomach was reflex, that is, spasm of the pylorus, whether secondary to appendicitis or disease of the gall-bladder or both, in addition to relief of the particular disease found, I have divided the muscle of the pyloric ring at the upper border in some cases also cutting away the superior attachment of the first 2.5 cm. of the duodenum and the last 2.5 cm. of the pylorus in the hope of separating the branches of the vagus at this point. I have doubly ligated and have divided between the ligatures 2.5 cm. above the pyloric ring on the side of the lesser curvature into the wall of the stomach so as to be sure to divide the branches of the vagi. More recently in discussing this problem with men who are examining the stomach röntgenologically, the fact was brought out that ulcers in the angle of the stomach cause the greatest spasm of the pylorus. Since then I have divided above the angle of the stomach the tissues of the lesser curvature well into the wall of the stomach, instead of as formerly at 2.5 cm. above the pylorus. It would seem to me that this slight addition to gastro-enterostomy or to other operations for the relief of reflex conditions has been of some benefit, but it will take observation of many cases and observations of many men in such conditions before much can be said as to the possible benefit to be derived from the procedure.

Certainly we know little concerning the exact functions of the involuntary nervous system which has a regulatory effect on all of these structures. What has been done in the past has been of great help but none of us is satisfied that we have reached the full acme of our surgical procedures for the relief of ulcer of the duodenum and ulcer of the stomach. Is success to come, then, through a better knowledge of the involuntary nervous system? At the clinic we feel that the dangers from ulcers in the stomach require their removal sometimes by excision of the ulcer and sometimes by partial resection of the stomach, with enlarging of the pyloric outlet or the making of a new one to the intestine. It may be expected, however, that any operation which secures adequate drainage, whether it be at the pylorus or by a new outlet or some form of resection will relieve the patient of symptoms. A small percentage of persons suffering with such troubles, however, have secondary trouble of the same nature. I expect more trouble if the free acid is high. The essential, however, is loss of balance between the acids and alkalis, whether they are high or low, relative overacidity aiding in pyloric closure.

With pyloric spasms the food naturally has greater difficulty in passing; perhaps more waves have to break against the sphincter before they can force it, perhaps the degrees of acidity above and below the opening have less influence than normal, and perhaps, as a result, the whole mechanism of pyloric control breaks down. A Rammstedt division of the pyloric muscle may often be beneficial.

THE PERITONEUM AS RELATED TO PERITONITIS

AN EXPERIMENTAL STUDY

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The remarkable lowering in mortality in general peritonitis during the last twenty years has been largely due to early diagnosis, prompt, speedy, and non-traumatic operation, which aimed to eliminate the source of infection and to establish drainage where necessary, and to the institution of proper after-treatment, which includes Fowler's position, maintenance of fluid balance, stomach lavage and in certain instances ileostomy. While further progress along these lines will undoubtedly take place, it seems probable that a better understanding of the pathologic processes involved might lead to principles most important in the treatment of peritonitis. Many complex problems present themselves. In general they may be listed as to the absorptive powers of the peritoneum; the problem of development of paralytic ileus and its influence on mortality, and finally the questions involved in the early circulatory failure so frequently observed in general peritonitis. The questions raised are far reaching and not easy of solution. Some progress, however, may be made by the study of isolated problems which go to make up the whole.

Last year[1] the results of some experiments dealing with absorption of bacillus coli from the normal and inflamed peritoneum were presented, at which time a review of the literature on absorption of fluids and the passage of solid particles and microörganisms from the peritoneum was presented.

While it had been known for many years that microörganisms passed into the lymphatics from the normal peritoneum, where they entered the blood stream through the thoracic duct, it had been doubted that direct passage of microörganisms into the blood stream from the peritoneum was probable. By isolating and draining the left thoracic duct and at the same time ligating the subclavian, internal and external jugular and innominate veins on both sides of the dog's neck, we found that bacillus coli introduced into the normal peritoneum appeared in the chyle in from five to sixteen minutes, in the peripheral blood in from twelve to eighteen minutes, and in the liver and spleen at about the same time, though in less numbers. It was therefore practically certain that bacillus coli was taken directly into the blood stream from the normal peritoneum.

The next question studied concerned the passage of bacillus coli from inflamed peritoneum. Different grades of non-infectious peritonitis varying from a hyperæmia to a well developed plastic exudate could be established

by intraperitoneal injection of turpentine emulsion. The passage of bacillus coli into the lymphatics and into the blood stream from the peritoneum was studied. It was found that in a well developed plastic peritonitis that the passage of bacillus coli into the lymphatics or into the blood stream was practically nil. Where the plastic exudate was absent or very slight, bacillus coli was taken up by the lymphatics and isolated from the chyle of the thoracic duct but no bacteria could be grown from the blood stream.

While all of the factors interfering with the passage of bacillus coli from the inflamed peritoneum may not be known, it can be fairly said that the presence of a plastic exudate in the peritoneum interferes very materially with the passage of bacillus coli into the chyle and seems to interfere entirely with the direct passage of these microörganisms into the blood stream.

The passage of bacillus coli from the peritoneum that contains a transudate was next studied. Hypertonic glucose injected into the peritoneum results in an increase in the volume of the fluid until it becomes isotonic. Starling [2] and his associates established the fact that the laws of osmosis govern the interchange of fluids in the peritoneum to the blood stream. We found that when bacillus coli was introduced into such an intraperitoneal transudate that the organisms appeared promptly and in large numbers in the chyle of the thoracic duct as well as in the peripheral blood stream. This point is of interest in connection with the rapidly fatal course of peritonitis developing in the presence of a transudate.

Working independently, Steinberg [3] and his associates conducted experiments along these same lines and in all important points their conclusions and ours coincided.

The object of this communication is to present the results of some experiments dealing with the question of the absorption of toxins from the normal and inflamed peritoneum in animals.

While the laws of osmosis governing the absorption of fluid solution of known crystalline substances are well known, the problem becomes more complicated when we consider the passage through the peritoneum of complex protein toxins. The literature gives us little help in this particular question. Achard and Gaillard [4] have shown that the higher the molecular weight of organic materials in the peritoneum, the lower will be the rate of absorption into the blood. Danielsen [5] concluded that while crystalloids are absorbed from the peritoneum through the blood stream that colloid substances are absorbed through the lymph channels. Fleisher and Loeb [6] performed nephrectomy or ligated the renal vessels and found an increased osmotic pressure of the blood and an increased rate of absorption from the peritoneum in those animals. They found no direct relation between diuresis and absorption from the peritoneal cavity. Pertinent to these observations, Starling points out that the osmotic pressure of blood proteins is related to the absorption of fluid by blood-vessels, in that by increasing protein concentration of a peritoneal saline solution, the absorbing force is reduced to the hydrostatic pres-

sure in the capillaries and absorption ceases. Bolton [7] concluded from his work that colloidal dyes indiffusible outside of the body pass through the peritoneum and capillary wall by diffusion directly into the blood, but slower than crystalloids. Colloids of a large molecular weight pass through much slower and it is probable that albuminous molecules are unable to do so. Klein [8] states that toxins of low concentration are absorbed rapidly from the peritoneum and that conversely, toxins of high molecular weight are absorbed very slowly into the blood.

Regardless of the above information, it is of course obvious that the very severe toxemia associated with general peritonitis must be caused in some degree by absorption of bacterial toxins from the peritoneum. It was our object then to select a toxin, even though its chemical composition is not definitely known, which could be identified after its passage from the peritoneum into the chyle or into the blood stream. Diphtheria toxin was selected because it could be obtained in large quantities and because of its known lethal properties when injected into guinea pigs.

The object of our experiments was to determine the absorption of diphtheria toxin from the normal peritoneum, the inflamed peritoneum containing a plastic exudate, and the peritoneum containing a transudate in dogs. Healthy adult dogs of medium size which had been fed on a fat diet were used.

ABSORPTION OF DIPHTHERIA TOXINS FROM NORMAL PERITONEUM

The question to be determined was whether diphtheria toxin in the peritoneal cavity passed into the lymphatics of the peritoneum, directly into the blood stream or both.

Experiment 1.—The thoracic duct was exposed in the neck and divided. The femoral artery was exposed and divided, the distal end having been ligated, the proximal end was closed with a vessel clamp so the blood could be obtained for culture. Two to five cubic centimetres of chyle and 25 to 40 c.c. of blood were collected and injected subcutaneously into guinea pigs for control. These animals lived. Ten c.c. of diphtheria toxin (Parke Davis) was then injected intraperitoneally through a trocar inserted midway between the symphysis and ensiform. Seventy-five c.c. of normal salt solution was also allowed to run into the peritoneal cavity to favor diffusion of the toxin.

10:20	Toxin and 75 c.c. salt solution injected.
	Chyle injected subcutaneously into guinea pig
10:30–11:10	2.5 c.c. injected.
	Pig died three days later.
11:10–11:40	7.5 c.c. injected.
	Pig died three days later.
	Blood injected subcutaneously into guinea pig
10:50	40 c.c. whole blood injected. Pig lived.
11:40	Dog bled to death. 60 c.c. of blood serum injected into pig subcutaneously.
	Pig died two days later.

Seven experiments of this type with substantially the same results were performed. In several the internal and external jugular, subclavian and innominate veins on each side were ligated to exclude the possibility of

accessory chyle ducts emptying into the blood stream. In one experiment only 1 c.c. of toxin was injected into the dog's peritoneum, in which case all of the guinea pigs survived who received the dog's chyle and blood. In several animals the injection of 25 to 40 c.c. of whole blood taken during the experiment caused the guinea pig to die in two to three days.

These experiments demonstrate that a known toxin injected into a dog's normal peritoneum passes directly into the blood stream as well as into the lymphatics in sufficient quantities to be fatal to guinea pigs. The concentration of the toxin and chyle seems to be greatest in about thirty minutes after the intraperitoneal injection of the toxin.

PASSAGE OF DIPHTHERIA TOXIN FROM THE PERITONEUM

It was found that intraperitoneal injection of 5 c.c. of a 10 per cent. turpentine emulsion on two successive days could cause a marked peritonitis with marked fibrin deposits and a serosanguineous fluid exudate. The passage of diphtheria toxin from such an inflamed peritoneum was studied in four dogs.

Experiment 2.—Forty-eight and twenty-four hours before the experiment 5 c.c. of a 10 per cent. turpentine emulsion were injected by hypodermic into the peritoneal cavity. On the morning of the experiment the thoracic duct and femoral artery were exposed as in Experiment 1. Control blood and chyle injected subcutaneously into guinea pigs did not affect them.

10:15	10 c.c. of diphtheria toxin and 50 c.c. of salt solution injected intraperitoneally through a trocar.
	Chyle collected and injected subcutaneously in a guinea pig
10:20–10:50	6 c.c. of chyle injected. Pig lived.
10:50–11:15	10 c.c. of chyle injected. Pig lived.
	Whole blood injected subcutaneously in a guinea pig
11:10	25 c.c. injected. Pig died eight days later.
11:20	Dog bled to death. 20 c.c. of blood serum injected subcutaneously into guinea pig. Pig lived.

An autopsy performed on the dog after the experiment showed a fibrino-serosanguineous exudate involving the whole peritoneum.

The results in all these experiments were substantially the same. It was somewhat more difficult to collect chyle as it was always found that chyle flowed very sparsely where a marked plastic peritonitis was present and instead of being milky the chyle was colorless and thin. None of the pigs receiving chyle died, whereas two pigs receiving whole blood died, one on the eighth day and one on the twelfth day.

We may conclude from these experiments that in a well developed plastic peritonitis caused by the injection of turpentine from the peritoneum of dogs, that the passage of diphtheria toxin into the peritoneum into the chyle is practically nil, that it passes into the blood stream in much smaller quantities than from the normal peritoneum. Indeed it may be questioned whether the pigs dying in eight and twelve days after the experiment really died from the effects of the toxin.

PASSAGE OF DIPHTHERIA TOXIN FROM THE PERITONEUM CONTAINING A TRANSUDATE

As is well known, the injection of hypertonic solutions into the peritoneum attracts fluid into the peritoneum. Several writers have advised the use of hypertonic solutions intraperitoneally in the treatment of peritonitis. The object of this experiment was to determine whether the injection of hypertonic glucose solution into the dog's peritoneum would influence the passage of toxin from the peritoneal cavity.

Experiment 3.—The day before the experiment 25 c.c. of a 50 per cent. glucose solution was injected intraperitoneally in medium size dog. The other factors in the experiment were arranged as in Experiments 1 and 2.

	5 c.c. of controlled chyle injected subcutaneously into guinea pig. Pig lived.
10:20	10 c.c. of diphtheria toxin and 50 c.c. of salt solution injected intraperitoneally.

Chyle injected subcutaneously into guinea pig

10:20–10:29	5 c.c. of chyle injected. Pig died.
10:30–10:40	6 c.c. of chyle injected. Pig died.
10:40–10:50	7 c.c. of chyle injected. Pig died.
10:55–11:05	6 c.c. of chyle injected. Pig died.

Blood injected subcutaneously into guinea pig

10:55	25 c.c. of whole blood injected. Pig died.
11:10	Dog bled to death. 20 c.c. of blood serum injected into guinea pig. Pig died.
	30 c.c. of blood serum injected into guinea pig. Pig lived.

At autopsy of the dog several hundred cubic centimetres of fluid were found.

This experiment demonstrates that the presence of a transudate in the peritoneum does not hinder the passage of the diphtheria toxin into the blood directly or by the lymphatics but rather favors the absorption by these routes. This fact is of interest in connection with the rapidly fatal course of peritonitis occurring in patients with ascites.

CONCLUSIONS

1. Diphtheria toxin passes promptly in considerable amounts directly into the blood stream as well as to the peritoneal lymphatics from the normal peritoneum of the dog.

2. Intraperitoneal transudate favors the prompt passage of diphtheria toxin from the peritoneum.

3. A plastic peritonitis markedly if not completely interferes with the passage of diphtheria toxin from the dog's peritoneum.

4. By analogy we may assume as a result of these experiments that when a plastic exudate is formed in the peritoneum, the passage of bacteria and toxin from the peritoneum is markedly interfered with. It would seem therefore advisable in the treatment of peritonitis to interfere as little as possible with the plastic exudate that is formed, as it can be regarded as a

favorable process. Perhaps it is unwise to press the analogy between dog and human peritoneum further, but one would feel from these experiments that in the early hours of peritonitis the factors of absorption of toxins and bacteria into the circulation directly and via the lymphatics was the dominant factor of danger, while later absorption from the peritoneum became less important and local conditions, such as paralytic ileus gained the ascendency in the picture.

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CHRONIC APPENDICITIS

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At various times during the last ten or fifteen years, we have all heard the last word spoken on "appendicitis" and it seems almost a waste of time to re-open the subject that has been so much and so thoroughly discussed. However, in studying the physiology and pathology of the ileocæcal coil from another standpoint, the so-called "chronic appendix" has forced itself into the picture so often that I am persuaded to present my observations to you with the hope that the 50 per cent. unrelieved by appendectomy may be benefited. We believe that in the disease known as "chronic appendicitis" the appendix may be implicated, but often is a small part of the condition, and that the removal of the appendix alone very frequently fails to relieve the symptoms for which the patient presents himself for operation. Failure to effect a cure has been so common that there is a growing tendency in the profession to charge the "chronic appendix" symptom syndrome to neurasthenia and to discourage surgery. This we think is as great a mistake as the simple appendectomy. We are sure that correlation of the embryological, physiological, and pathological factors will lead us nearer to the etiology and therefore the logical treatment.

"Harvey [1] makes four main subdivisions in the journey which the cæcum makes from its inception to its final lodgement in the right iliac fossa, namely: *Migration, rotation, descent,* and *fixation.* In the fifth week of fetal life, the primitive gut is attached to the umbilicus and the cæcum is beginning to show as a bud on the caudal portion of the gut. As the liver at this stage rapidly increases in size, the bowel is pushed out of the cœlum into the umbilicus. Next the relative increase in size of the body cavity permits the return of the gut. The small intestine is the first to return and the large bowel follows. The junction of the small bowel with the large is forced by the small intestine into the upper right quadrant and at this stage the small intestine enters the large from the right and above. This ends the migration. The next stage is that of *rotation,* resulting in the entrance of the small bowel on the inner side, or from the left and below. *Descent* starts at this point and in the latter months of fetal life and first month after birth, the growth of the organ carries it and the ileocæcal valve into the lower right quadrant. Fusion of the various mesenteries results in the position which is termed normal in the adult life. It is well to note that the descent and fusion are relatively late stages in the developmental cycle. Studies in comparative anatomy would indicate that fusion is doubtless a result of the assumption of the erect posture of mankind, and it is just to suppose that on the success of these last two

processes, will depend to a considerable extent the ability of the bowel to function properly."

The external longitudinal muscle fibres of the colon are gathered into three distinct longitudinal muscular bands, which lift the cæcum many inches in a so-called normal ascending colon, pulling from the first fixed point, the hepatic flexure, and are largely concerned in the normal mechanism of emptying the cæcum.

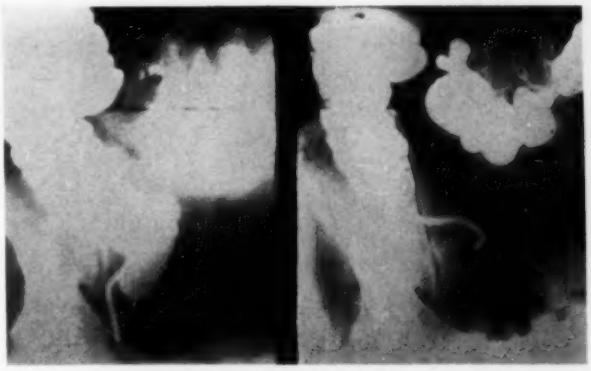

FIG. 1.—Showing haustrated cecum in normal position with patient supine. Completely rotated unhaustrated cecum descended into the pelvis with patient standing.

The intestinal wall carries within *itself* the mechanism essential to peristalsis. The law of peristalsis of Bayliss and Starling was worked out experimentally on the dog, with a balloon in the *small* intestine attached to a manometer. It was demonstrated that pinching the intestine just above the balloon, caused a cessation of peristaltic activity and a dilatation of the intestine from eight to twelve inches below the pressure; that pinching of the intestine behind the balloon caused a spasticity and great increase in peristalsis ahead of the pressure. Our observation reverses this process in the colon. In other words, pressure upon a ganglion contained in the wall of the colon causes dilatation behind and spasticity in the front. This is our conception of the production of the thin-walled, blue, atonic cæcum. With a mobile cæcum and ascending colon, due to faulty fusion, the terminal event in the embryologic cycle, we have the ideal condition for the development of a long chain of events. Beginning with loss of tone, due either to advancing years, a long strain or a long physical illness, we have a loss of the lumbar curve, which is the shelf on which the normal cæcum lies. With the loss of the lumbar shelf, we have a tendency of the cæcum to prolapse. Nature in her effort to lift up a prolapsing organ starts the growth of a membrane at the site of the right colic artery on the

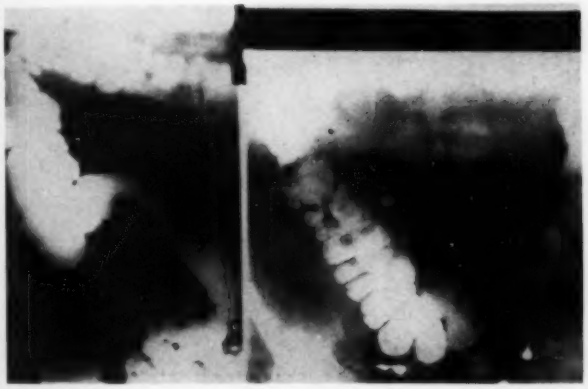

FIG. 2.—The same change of position of the cecum supine and standing except that in this case there is no pericolic membrane; the cecum descended retains its haustrations and causes no symptoms.

mesenteric side, which attaches the colon tightly to the side wall by a reduplication of the peritoneum. This was first described by Jackson many years ago and is generally known as "Jackson's Membrane". As this attachment becomes tighter, the colon is rolled to the right and twisted, the prolapsing heavy cæcum swings forward and to the left exaggerating the twist. This twist so pinches the intestinal wall containing Auerbach's plexus that cæcal dilatation with lack of peristalsis follows, and a spastic colon *forward* from the point of pressure develops. This paralysis of the cæcal muscular walls due as we think to plexus pressure is at first intermittent, occurring when the patient is erect and disappearing when prone, making it easy to miss, either in routine X-ray examination or on the operating table.

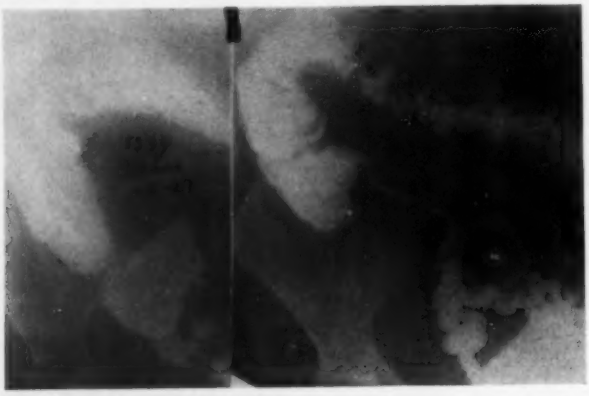

FIG. 3.—Cecum turns inward, and fixed by adherent appendix causes obstruction at site of pericolic membrane when the cecum descends when the patient is erect.

We feel that here we have the formation of a vicious circle. As the cæcum becomes heavier the strain increases at its point of fixation, a pericolic inflammation due to strain tightens the band, so that eventually the obstruction may become anatomical as well as physiological. There is often a retrocæcal appendix, in many cases an undescended appendix, which draws the cæcum sharply up to the right, so that that part of the intestine which appears to be cæcum in the X-ray study is really the middle of the ascending colon. This, the retrocæcal appendix, is usually included in the adventitious attachments of the ascending colon.

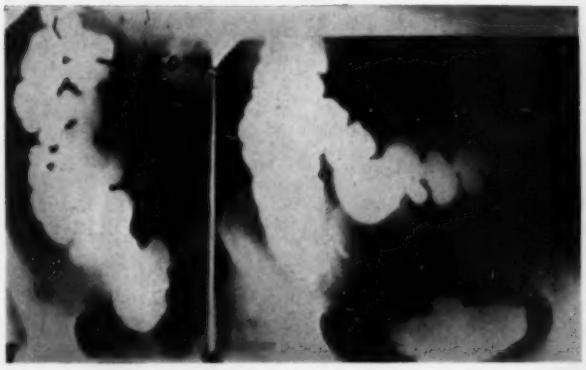

FIG. 4.—Cecum fixed and turned inward by an adherent appendix when patient is erect, but retaining its haustrations, when it descends, as there is no pericolic membrane.

Actual mechanical fixation of any part of the cæcum or ascending colon interferes with the direct pull of the longitudinal bands from the normal fixed point at the hepatic flexure, and so prevents the lifting of the cæcum.

This theory is based largely on deductions from clinical observation at the operating table and in the X-ray laboratory. We have demonstrated so many times that it is no longer a cause for remark, that this toneless cæcum,

unhaustrated, dilated, and thin-walled, appearing to have no muscle, is capable of an *immediate* return in color, thickness and peristaltic activity. This *immediate* return of peristalsis upon removal of the plexus pressure must disprove the theory of Lane that the cæcum has become toneless through atrophy of muscle from *hydrostatic* pressure, and the theory that the muscle has atrophied through tropic changes from long toxemia. Also this disproves the theory of ordinary anatomical intestinal obstruction in the ascending colon. For in all parts of the intestinal tract a simple partial anatomical obstruction gives rise to increased peristaltic activity and hypertrophy behind rather than atony and dilatation.

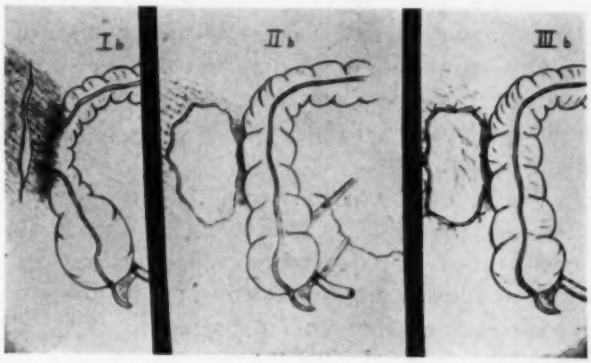

FIG. 5.—I. Showing pericolic membrane incised at its junction with the parietal peritoneum. II. Colon rolled out. III. Denuded surface covered with free omental graft.

With the colon pulled tightly to the left, the assistant holding the flexure in one hand and the cæcum in the other, the reduplicated peritoneum is divided with a sharp knife at the white line, which marks its junction with the parietal peritoneum, the ascending colon immediately becomes straight. The edges of the longitudinal incision in the peritoneum are separated four or five inches by the rolling out of the colon, which has been compressed over the right kidney. The cæcum immediately draws up, regains its pink color and contracts when pinched between the gloved finger and thumb. We plant in this denuded area a free omental graft, carefully stitching the omental edge to the edge of the peritoneal incision. Interposition of tissue apparently prevents reformation of the constricting membrane as we have never re-operated one for adhesions in a series of more than two hundred cases scattered over a period of ten years.

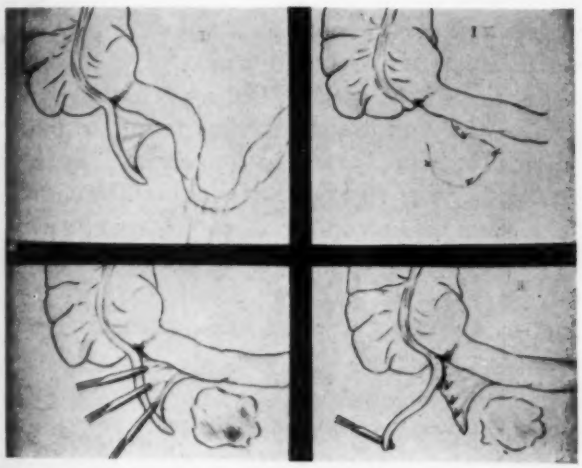

FIG. 6.—Method of utilizing spread-out meso-appendix to cover denuded area on mesentery after division of "Lane Kink".

These typical cases with the mid portion of the ascending colon rolled to

the right and attached to the parietal peritoneum, would seem ideal for cæcal fixation to prevent descent and twist.

We have been unable to find a method of fixation which may not defeat its own object by interfering with peristaltic waves which are necessary for the emptying of the cæcum, and prefer to reproduce the mobile cæcum and depend upon external support to prevent the band from reforming.

Our experience has taught us that the prolapsed cæcum is comparable to the prolapsed stomach—it will empty from any position if the whole organ prolapses and if peristalsis is not interfered with by some other cause than position.

We have become convinced that the symptom syndrome, usually called "chronic appendix", is almost always due to interference with cæcal peristalsis, rather than appendicial inflammation. In fact we feel that without a history of sharp attacks accompanied by fever and vomiting, a diagnosis of chronic appendicitis can not be made. The reflex stomach symptoms are caused in our opinion by recurring temporary intestinal obstructions, partial or complete, due to the twisting of a loaded cæcum over a fixed point. And only those cases in which the undescended appendix is retrocæcal, and its delivery releases the colon fixation or in which the appendix alone cripples the cæcum, is there symptomatic cure, following a simple appendectomy.

This condition is easily demonstrated by gastro-intestinal study by the method of Taylor.[2] He routinely examines the ileocæcal coil for mobility as well as motility. He makes observations at six, nine, twenty-four, and forty-eight hours—both erect and supine. He finds as I will show you with slides that there is a change of location of the loaded cæcum of from six to eight inches with a change of position of the patient; that a perfectly normal appearing colon with the patient supine will drop to the bottom of the pelvis when observed standing. And he is convinced that a barium enema is entirely worthless as a means of diagnosis of most right-sided conditions. The first sign is a distinct break in the barium column in the ascending colon with a mass movement of the barium forward from the point of break, leaving an unhaustrated packed cæcum.

Clinical Analysis.—Taking for analysis 571 consecutive cases diagnosed "appendicitis" on which I have operated.

One hundred were acute; 51 were sub-acute—these can be disregarded.

Of the remaining 420 cases, diagnosed "*chronic* appendicitis":

Seventy-two only had a history of a previous sharp attack.

One hundred and sixty-five had pyloric spasm described as stomach symptoms.

Of these, 8 had duodenal ulcer.

And 38 a diseased gall-bladder discovered at operation and operated upon at the same time or subsequently.

All had constipation varying in degree.

Seven had history of colitis with occasional attacks of diarrhœa.

All had a spastic colon as demonstrated by the röntgenologist.

The appendix only was removed in 202 cases, just less than 50 per cent.

One hundred and eighty-six had a distinct pericolic membrane, crippling the cæcal peristalsis and causing a cæcal block.

Of these, thirty-two had had a previous appendectomy without symptom relief.

Fifty-eight had the terminal ileum bound down as described by Lane and termed "Lane Kink".

Fourteen had had a previous appendectomy without symptom relief.

Seventy-six cases were found at operation to have retrocæcal appendix.

In 34 of these the appendix alone was removed, the crippled cæcum being released by its removal.

In 35, a binding down of the mid-portion of the ascending colon by a pericolic membrane was dealt with separately.

In 3, an appendix and upper abdominal lesion were found.

And in 4, the appendix, pericolic membrane and upper abdominal lesions were present.

We feel that in this series of 420 cases of chronic appendicitis, only 202 had a right to relief of symptoms, if the appendix alone had been removed; that in the remaining 218 cases it was necessary to deal with the other pathology encountered in order to expect a symptomatic cure. My especial interest is in the group of 186 cases complicated by the pericolic membrane which I think is usually not recognized and not disturbed at operation. I feel that this condition associated with the pathological appendix must be dealt with just as definitely as gall-stones or ulcer in order to relieve the patient.

Closing Discussion.—Dr. Rea E. Smith (Los Angeles, California): Doctor Jones asked as to the end results of the 220 cases. I am embarrassed to answer that question. I left out end results because my follow-up is not perfect. I was unable to find any patient in this series in whom the symptoms persisted after operation. But I am sure that must be due to the fact that I could not hear from them all. However, our office is free from the chronic unrelieved patients that we had in the old days when we did appendectomy alone for chronic appendicitis.

In conclusion we believe that the symptoms that we are accustomed to call "chronic appendix" have a larger pathology than appendicial inflammation; that simple appendectomy will cure less than fifty per cent. of these cases; that these symptoms are caused by a distinct surgical disease and are not to be laid to the door of neurasthenia, and that symptomatic relief may be obtained surgically in the same high proportion of cases as is obtained by surgery upon the diseases of the gall-bladder, the stomach, and the duodenum.

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DISCUSSION: DR. CHARLES L. GIBSON, New York City, said that the most astonishing thing in their original follow-up of six years was the shocking discovery of their very bad results in chronic appendicitis—if he remembered correctly, 30 per cent. This led them to investigate why they were getting such bad results. Practically they had no bad results in operations for acute appendicitis, that is, the patients coming back after operation for acute appendicitis are practically immune from any complaints, and yet here are the other class who come back full of complaints.

They have reduced bad results largely by operating on conditions under their right name, that is, they study their cases very much more thoroughly, and particularly in the diagnosis of chronic appendicitis in women. As a matter of fact, very often they operate on so-called chronic appendicitis as a prophylaxis against acute appendicitis. Certainly in his hospital service he has four times as many operations for acute appendicitis in men as in women, and yet it is these unfortunate women who get operated on for chronic appendicitis.

When a patient comes in with symptoms seemingly pointing to chronic appendicitis, they try to get away from that diagnosis as far as possible and try to exhaust every other possibility. One of the elements is a thorough history. The service is handicapped by so many foreigners, ignorant recent immigrants, a very distinct handicap. Some of the bad results have been particularly in those cases where they had been unable to get a full history. These patients nowadays are thoroughly studied, and studied especially fluoroscopically.

A second way in which they had improved their results has been by doing a surgical operation. He did not call taking the appendix out through a tiny hole a surgical operation. Some of their earlier results he thought might be attributed to that. The appendix was simply pulled out and removed without any exploration. Every operation for chronic appendicitis should be an exploratory laparotomy, removing not only the appendix but investigating the rest of the abdomen and remedying the conditions present. Many conditions can be remedied, especially in women; very often diseased pelvic organs that could not be recognized short of a laparotomy.

BEZOARS

WITH THE REPORT OF AN ADDITIONAL CASE OF PHYTOBEZOAR

By Urban Maes, M.D.

of New Orleans, La.

A single case report as the raison d'être of a clinical paper is rather deserving of an apology and certainly deserving of an explanation. In this instance, however, I believe that my reason is fairly obvious, the desire to call attention to a condition which is almost entirely ignored by text-books and systems of medicine and which, although rare, is a possibility always to be considered in the diagnosis of obscure gastric conditions.

Bezoars are by no means as rare as they were formerly supposed to be. From 1779, when the first case (a trichobezoar or hair ball) was reported by Baudamant in the *Journal de Médecin*, until 1914, when Matas' classical paper was read, only seventy-six cases had been reported in the literature. In 1921 Davies reported thirty-two additional cases, and since then others have been reported by Barkeley, Carr, Doolin, Harris, Herzfeld, Neely, Netto and Whitteman, making in all one hundred sixteen cases. Hart, in 1923, added eight cases of phytobezoar to the five already reported, and since then, in addition to the case I am now reporting, others have been added by Hamdi (three), Porter and McKinney (two), Tschassownikoff, Larimore (two) and Upson, bringing the number of this type to twenty-three.

It is quite probable, as Matas suggests, that the total would be materially increased if a canvass could be made among surgeons generally and if the many unreported cases which undoubtedly have occurred were thus brought to light. It is even more probable that many cases exist undetected, especially in rural communities, where X-ray facilities, which offer the only sure method of diagnosis, are generally lacking. Simon, in a discussion of Hart's paper, called attention to the fact that such foreign bodies may be the real explanation of many supposedly inoperable gastric carcinomata which have been diagnosed only clinically, and suggested also that they might explain many fatal instances of perforation supposedly due to ulcers. The latter supposition is especially valid in view of the fact that Butterworth's case, as well as several others reported, was of this sort, the diagnosis being made only at autopsy.

The term bezoar is generally applied to concretions found in the stomach and intestines of animals, and the reader who is interested in the historical and archeological aspects of the subject is referred to the report of Matas already quoted, which was read before the Southern Surgical Association in 1914. Hair balls or trichobezoars are particularly common in the cow, the horse and the cat, especially during the hair-shedding seasons. Often they

are vomited or are passed per rectum, but even if they are retained they are apparently without harmful effects. This type of bezoar is the one most commonly found in humans, and the majority of the reported cases are in young girls of the English-speaking races. To date only two cases have been reported in males; in the first instance the man was found to be chewing his beard, in the second the man was insane and when the tumor was removed surgically it was found that hair played only a minor part, nails, wire and other such objects making up its bulk.

FIG. 1.—Photograph of tumor.

Formerly the common explanation of these tumors was the obvious one, that young girls with long flowing hair were prone to play with it and might end by swallowing bits of it, but with the advent of universally bobbed heads such an explanation is no longer tenable, and it will be interesting to observe whether the incidence of trichobezoars will be lessened in this generation. Some psychic or neurologic factor is unquestionably at work in such cases as that reported by Neely, for instance, in which a patient from whom a trichobezoar had been removed surgically began to eat her hair again before her discharge from the hospital. Even more remarkable in this regard is the case reported by Harris, in which within fourteen years five operations were performed on the same patient for the removal of such masses; in the last operation the tumor was found extending into the duodenum and weighing two and a half pounds. As a rule, however, when the psychic factor is apparent, the tumor contains string, cotton and other materials manifesting a truly perverted appetite.

Trichobezoars, unlike phytobezoars, are constantly added to as additional hair is swallowed, and they may attain considerable size, the one reported by Davies, the largest on record, weighing six and a half pounds. They may extend into the duodenum and detached masses may be found in the ileum. Digestion is generally good until the mass completely fills the stomach, probably because the bulk of the food taken is normally subject to extragastric digestion, and the tumor, being compact, does not absorb it in its passage through the stomach. Ultimately there is pain, vomiting, constipation alternating with diarrhœa, foul breath, anemia and exhaustion. A rather remarkable and quite uniform finding in most of the reported cases is that, until the last stages, the patient's nutrition and vigor are only slightly

impaired. Death finally occurs from inanition, intestinal obstruction or perforation.

Phytobezoars, or fruit and vegetable tumors, are composed chiefly of persimmon, prune or raisin seeds and skins, or of celery and salsify fibres, together with starch granules, fat globules, muscle fibres, elastic tissue, fatty acid crystals and epithelial cells. The etiology is obscure and such explanations as have been advanced are entirely speculative. Both hypoacidity and hyperacidity have been suggested as causes, but the gastric analyses in the reported cases are still too few and their variations from the normal are too slight to warrant drawing any conclusions from them. Another explanation is that the high percentage of gum and of pectin (14.1 per cent. and 7 per cent. respectively) in persimmons favors cohesion, while the muscular action of the stomach, initiated by the ingestion of food, easily molds and compresses the already coherent mass; the excessive muscular activity induced by the consequent acute gastritis then completes the process, so that the tumor remains intact even after the cohesive substances have been removed by the normal digestive mechanism. Granting the correctness of this assumption, it is still not clear why the condition should occur only in certain individuals, who must comprise surely a negligible number of those who consume these very common foodstuffs.

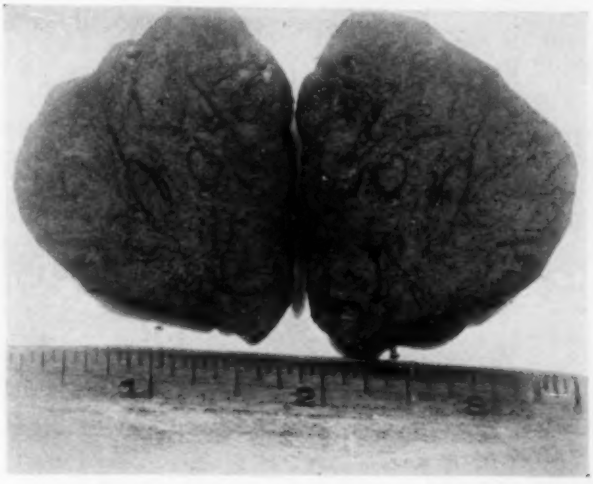

FIG. 2.—Photograph of tumor on section, showing of persimmon seeds and hulls.

The symptom complex is always that of an acute gastric disturbance, with pain which tends to be paroxysmal in character the chief feature. In most of the reported cases the pain tended to persist, though to a minor degree, between attacks, and it was both increased and decreased by eating. In some instances it was little more than a sense of fulness in the epigastrium. Vomiting is not usually marked. When it does occur, it is mucous or watery, because the bezoar acts as a ball-valve in the cardiac opening and prevents the full ejection of the stomach contents. The acute pain, on the other hand, is due to a similar obstruction at the pyloric opening which results in the retention of the food within the stomach. As is the case with trichobezoars, the most striking feature of the syndrome is that in spite of the persistence and the severity of the symptoms, the patient's general health remains good, there is rarely great loss of weight, and the nutrition is prone to remain unaffected.

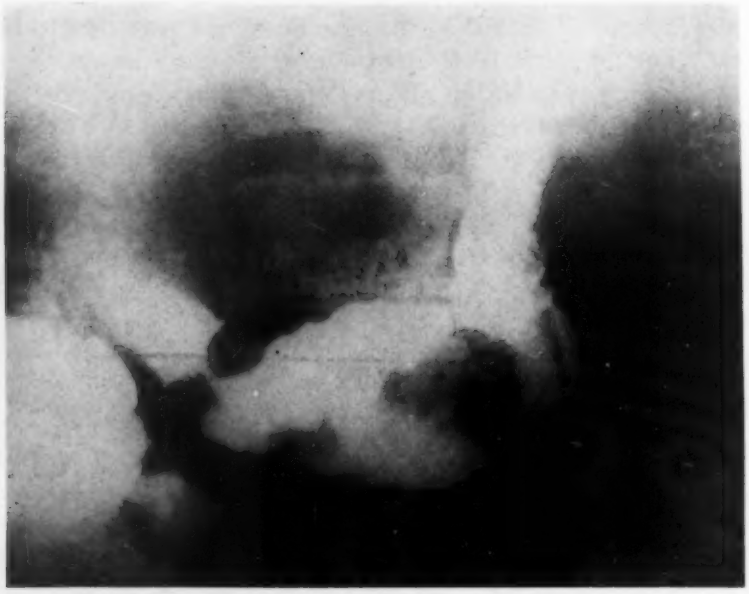

FIG. 3.—Radiogram of stomach showing filling defect.

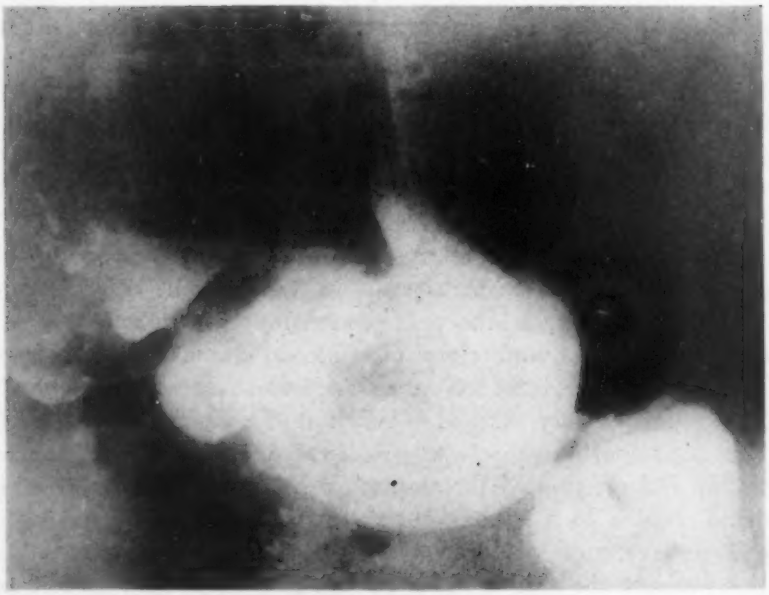

FIG. 4.—Same, with filling defect being displaced by external pressure.

Two other types of bezoar are classified by Hart, the trichophytobezoar, a combination of the two varieties we have just described, and the shellac concretions, often of large size, found in painters and furniture workers who have swallowed the shellac solution used in their work, presumably for the sake of its alcoholic content.

Until the advent of the X-ray the pre-operative diagnosis of bezoars was seldom made correctly, though now, with the proper employment of this facility, it is almost impossible to miss it. The history is not helpful unless a story of hair-eating or of the ingestion of certain types of food is definitely elicited, and this does not usually happen unless the possibility is borne in mind and the patient is specifically questioned on these points. The presence of the palpable mass suggests malignancy, though the acuteness and duration of the symptoms and the generally good condition of the patient are against this. It is always possible, of course, that other pathology may exist and may cloud the issue, as in Larimore's case, in which the phytobezoar was entirely overlooked because a previous cholecystectomy with subsequent pyloric and duodenal adhesions had destroyed the mobility of the tumor and confused even the X-ray findings.

FIG. 5.—Same, tumor pushed up into cardia, and therefore not visible.

As a rule, however, the radiographic findings are constant and definite. The mass lies free in the gastric cavity, where it is seen as a shadow or as a lighter area amid the darker area of the barium which outlines and coats it. Under the fluoroscope it can be made to change its position freely on palpation. Later examination discloses a normally empty stomach except for the barium-streaked, freely movable tumor. Barium must always be administered, for simple anterior-posterior examination does not give constant findings. The efficacy of the X-ray as a diagnostic agent is the undoubted explanation of the increasing number of cases of bezoar reported

within the last decade; it would be unreasonable to suppose that their incidence is increasing.

The treatment is essentially surgical. Massage has been advised but it is obviously unreliable, quite aside from the fact that the possibilities of danger inherent in such a method do not warrant its serious consideration. Likewise digestants do not commend themselves, for it would seem that any agent strong enough to affect the tumor is likely first to injure or even to destroy the more delicate gastric mucosa. In fairness, however, the case of Mills and Simpson, quoted by Hart, must be mentioned, in which a phytobezoar was dissolved by dilute hydrochloric acid, the diagnosis being confirmed both before and after treatment by X-ray examination.

Surgery, therefore, is the preferred treatment, with the technic in the main that of the usual gastrointestinal operation. The incision should preferably be along the anterior wall of the stomach, where the vascularity of the tissues is least, and should be sufficiently large to permit the easy removal of the tumor. Drainage is seldom indicated, though naturally every precaution should be taken to protect the peritoneal cavity from the spill of the stagnant and often decomposing gastric contents. Careful exploration beyond the stomach is always indicated, and enterotomy should be done if additional masses are found in the small bowel. I have made no effort to figure the operative mortality in the cases reported since Matas' paper was written, but from casual observation I would say that it cannot exceed the 4 per cent. stated by him for the forty-seven operative cases reported to that date.

Case Report.—A. G., a fifty-seven-year-old white merchant, from one of the rural communities of Louisiana, was seen by me in June, 1927, at which time he complained of abdominal pain which had persisted for two and a half years. The first attack had been ushered in with acute, cramping abdominal pain, so extreme that relief was finally obtained only after the administration of morphia several hours later. There had been no nausea or vomiting. Since that time similar attacks had occurred at intervals of from one to three weeks, always with pain the dominant feature; at times the ingestion of food or even of a hot drink gave relief, but usually morphia was required. In the interval he was perfectly well except for some shortness of breath, most evident after meals and without relation to physical exertion. The general health was good and there had been no marked loss of weight.

Physical examination disclosed a small, freely movable mass in the upper abdomen but otherwise was entirely negative. The condition, largely due to the character of the pain, had previously been variously diagnosed as acute gastritis, gall stone colic and angina pectoris, but in my opinion the presence of the mass rather suggested malignancy, particularly in view of the patient's age, though I was obliged to grant that its apparent free mobility, the acuteness and duration of the symptoms and the excellence of the patient's general health were all against this supposition. It was not until X-ray examination was done that the true condition was revealed, and it is entirely due to the discernment of Dr. W. F. Henderson, radiologist at Touro Infirmary, that the correct pre-operative diagnosis of phytobezoar was made. The findings are so typical of all such cases that the report is appended in full:

"At the entrance of the first bolus of barium into the stomach it is observed to strike upon a large oval mass and to pour downward from it, and each succeeding swallow of

barium manifests the same phenomenon. As the barium is ingested, the stomach fills around this globular mass, leaving a punched-out area in the median portion. Manipulation with the gloved hand causes this to pass very freely down to the pylorus, and subsequently it can be forced into the extreme fundus of the stomach, where it remains for a time, only to pass again into the median segment. The mass changes its position with changes in the posture of the patient, and no incisura or niches in the gastric walls can be observed. It is believed that were a pedunculated tumor present, traction upon the pedicle would compel distortion of the gastric wall. It is therefore considered that this mass is free in the stomach and is most probably a phytobezoar. The duodenal bulb is free from pathology, as is the remainder of the gastrointestinal tract. It is interesting to note that specific questioning of the patient reveals the fact that persimmons were eaten on the day from which he dates his illness."

The patient later added further details of the onset of his illness. While hunting he had thrown himself under a persimmon tree to rest and had gorged himself with the ripe fruit lying beneath it, afterward drinking copiously of spring water. The attack, as previously described, had ensued almost immediately.

The further history is without special incident. Laparotomy through a left rectus incision exposed the stomach and permitted the palpation of the floating intragastric mass, which was removed without difficulty through a typical gastrotomy opening in the anterior wall. The patient's recovery was uncomplicated and his cure has been complete.

The mass removed had a very foul odor. It was dark brown, hard and roughly spherical, and exhibited a sort of mosaic appearance due to its composition of persimmon skins and seeds held together by some cellular material of undetermined origin. It weighed 386 grams and measured roughly two by three inches. The presence of the fruit on the surface showed that the mass had formed promptly after the ingestion of the persimmons and that no other material had since been added to it.

Every feature of this case is typical, and had the possibility been borne in mind and the patient specifically questioned, the diagnosis could probably have been made, at least tentatively, even before X-ray examination was done.

SUMMARY

1. A case of phytobezoar is reported, with the idea that the condition, though admittedly rare, is being overlooked as a possible cause of obscure gastric disease.

2. Trichobezoars (hair balls), phytobezoars (skin and seed balls), trichophytobezoars (a combination of these two) and shellac concretions are possible types of bezoar.

3. These all give rise to varying degrees of gastric distress. Pain is usually a marked feature and the general nutrition is surprisingly little affected.

4. The X-ray offers the only definite means of diagnosis and its aid should be invoked in all instances of obscure gastric disturbance.

5. Surgery is the only safe and effective treatment.

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NOTE. This bibliography supplements the one attached to Matas' article "Hair balls or hair casts of the stomach and gastrointestinal tract", which appeared in *Surgery, Gynecology and Obstetrics*, November, 1915, vol. xviii, pp. 594–608. I am indebted to Miss Mary Louise Marshall, assistant librarian of the Orleans Parish Medical Society, for its preparation.

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Discussion: Dr. Vernon C. David, Chicago, Ill., remarked that these persimmon balls may perhaps be more common in certain regions of the country than is generally appreciated. He had seen one which was about half the size of an ordinary building brick, which was removed from the stomach. He reported that case to the Western Surgical last year, and in the discussion there must have been at least fifteen or twenty members of the Society who had seen cases of that kind although the literature does not report very many of them. He felt that the further publicity of such facts may be useful in early diagnosis and proper understanding of the situation.

Dr. Emmet Rixford, San Francisco, Calif., recalled that the Chinese utilized the principle of "similia similibus curantur" long before Hahnnemann. In fact, it goes back well beyond the Christian era. One of their remedies was to use bezoar stones which were found in animals as a sovereign remedy against cramps.

ADAMANTINOMA

By Channing C. Simmons, M.D.
of Boston, Mass.

From time to time articles on adamantinoma (adamantine-epithelioma, cystosarcoma, adeno-carcinoma, epithelial odontoma, etc.), appear in the literature, and from the few cases reported it would appear that the tumor is comparatively rare. As a matter of fact, it is apparently not uncommon, but is often confused with bone cysts, benign giant-cell tumor, or carcinoma. Most of the published articles are reports of two or three cases with a discussion of the origin and formation of the tumors. For a review of the pathology and a complete bibliography, the reader is referred to recent articles by Bump[1] and Murphy.[2]

Fig. 1.—Case 11, male, sixty-two years of age. Tumor of one year duration. X-ray shows cystic tumor in the ramus of the lower jaw near the angle. The typical appearance has been somewhat masked by secondary inflammatory changes. Death nine months later from local extension of tumor and sepsis. (See Fig. 2.)

The present communication is based on twelve cases seen at the Collis P. Huntington Memorial and the Massachusetts General Hospitals. All of these cases have been seen or operated upon by the author. Two other cases in which the clinical diagnosis of adamantinoma was made were observed, but pathological material was not available and they have been excluded. Microscopic sections from nine of the twelve cases reported were available for review, while reports from competent pathologists were obtained in the remaining three.

To understand these tumors and recognize the different types, a clear knowledge of their formation is necessary. The tumors arise in the jaws, the lower more often than the upper, from the remains of the enamel organ, or from the paradental epithelial debris. Similar tumors of congenital origin are occasionally seen in the region of the hypophysis. (Peet.[3]) In the formation of the tooth, all parts are of mesoblastic origin with the exception of

the enamel. This is derived from an infolding of the epithelium covering the gum, the formation of the enamel organ being analogous to that of a gland. The connective tissue surrounding this ingrowth proliferates forming the dental bulb on which the enamel rests. These tumors arise from the cells of the enamel organ or the epithelial rests in the immediate vicinity, also derived from the infolding of the buccal epithelium. The epithelial cells differentiate to a greater or less degree and the tumors, therefore, vary in their appearance. If the epithelial cells are only slightly differentiated and

FIG. 2.—Photomicrograph of Case 11. (See Fig. 1.) The epithelial cells show little differentiation and the appearance of the section closely resembles cancer. Columnar cells are seen, and in other sections from the same tumor, enameloblasts could be found.

in solid masses, the general appearance microscopically is that of carcinoma. In certain instances the cells have a glandular arrangement and may resemble the malignant adenoma of the salivary glands. If differentiation of the original epithelial cell to the enamel cell has progressed farther, the cells are cylindrical and star-shaped cells or true enameloblasts are seen.

Although in a given tumor all the cells may be of one type, it is usual to find cells presenting all degrees of differentiation. There is also a certain amount of proliferation of the surrounding connective tissue, and other mesoblastic tooth elements are often found in the tumors. In fact connective tissue proliferation may overshadow the epithelial tumor and the section appear at first glance as a fibrosarcoma.

Three types of epithelial cells are described: (1) Cells of cuboidal shape which may present prickles characteristic of squamous-cell carcinoma, and can easily be mistaken for that tumor. (2) The tall columnar cells having

an alveolar arrangement and forming a tumor commonly described by pathologists as cylindroma. (3) Stellate cells which are characteristic of the enamel organ. These three types of cell represent different phases in the differentiation of the cells from the original pavement epithelium of the gun to the enamel.

In gross, the tumors appear as multiple cysts centrally placed in the jaw, varying up to two or three centimetres in diameter and associated with a certain amount of solid tissue. The cysts expand the jaw, destroying the cortex. If the tumors obtain a large size, there is marked deformity and they may present under the mucous membrane of the alveolar process as a fluctuating area. In the lower jaw they usually arise near the angle.

FIG. 3.—Case 14, female, fifty-eight years of age. Tumor of jaw of seven months' duration. X-ray showing the multiple cystic tumor of the lower jaw.

The impression obtained from reading the literature is that the tumors are benign and although this is usually true, the growths are epithelial in origin and potentially malignant. Bloodgood[4] states that the tumors do not metastasize in the true sense of the word, but that implantation metastases in the soft parts may follow incomplete removal. Bump found only two cases of glandular metastasis in the literature. (Reported by Ewing.) It is probable that the malignancy varies as in cancer according to the amount of differentiation of the cells, but this series is too small to allow of conclusions being drawn. In two of the twelve cases, however, there were glandular metastases. These occurred late, were regional at first and, in the one case in which they were general, dissemination was not demonstrated until fourteen years after the onset of the disease. Sections of a metastatic gland and of the primary tumor were available for study in both of these cases. In Case II the glands in the neck appeared twelve years after the original tumor. In the primary tumor cells of all types could be found, while in the gland the cells were more differentiated. This patient is alive without evidence of disease eight years after resection of the jaw and dissection of the glands of the neck. (Fig. 5.) In Case VII the tumor in the gland was similar to the primary growth. The tumor was of the adenomatous and

cystic type with prickle cells, columnar cells, and a certain number of enameloblasts. The patient died fifteen years after the tumor was first noticed, with metastases in the glands of the neck, and lungs. Both of these cases had been operated upon several times.

A third case (Case X) presented clinical evidence of metastases in the glands of the neck, but his general condition contraindicated operation, and it has been excluded as no specimen was available for study.

The tumors are of very slow growth, the average duration of the disease in this series from the time the tumor was first noticed, until the patient was examined at the hospital being nine years. The shortest duration was seven months (Case III), while five were over five years, one being twenty-five years. The individual cases vary greatly in duration and course. In Cases I and III, the duration of the disease from the first symptom to death from local extension and sepsis was less than two years. In both of these cases the cuboidal type of cell predominated, and in fact, one was diagnosed twice as cancer and twice as adamantinoma by the same pathologist. In Case IV the duration from onset to the last observation was thirty-five years. Four operations had been performed on this case, each followed by immediate recurrence. X-rays had been taken yearly for the last ten years and showed no change in the tumor, and operation was finally performed for compound pathological fracture of the jaw. Microscopic examination of the specimen removed at the last operation showed the same structure as the tumor removed twenty-three years before. The growth was cystic in character and the cells almost entirely of the stellate form.

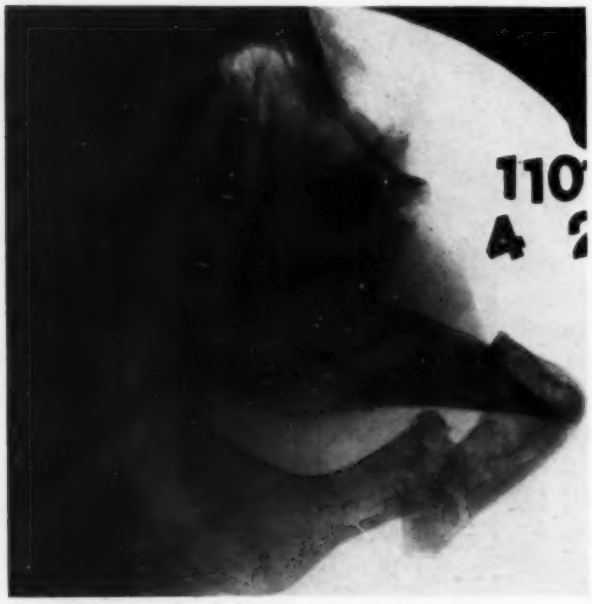

FIG. 4.—Case 4, female, fifty-six years of age. Tumor of lower jaw for thirty years. Four operations followed by recurrence, the first having been performed twenty-three years previously. X-ray shows compound pathological fracture through the tumor. (See Fig. 5.)

The usual history was that of a tumor of the jaw of slow growth without symptoms, which had had several minor operations performed on it, followed by immediate recurrence. In many instances it was obvious that the correct diagnosis had not been made by the physicians previously consulted. Several of these patients had been treated by dentists on the supposition that the cavity seen in the jaw by the X-ray represented a tooth abscess. Ten of the

twelve cases had had some previous operative treatment varying from extraction of teeth or excision and drainage of the cyst, to partial removal. Case IX had not been operated upon but had received radiation treatment with temporary improvement.

Specimens from nine of the cases were available for review and represented types of all tumors described pathologically. Certain of the tumors were composed of multiple large cysts (Cases IX and XIV) while others (Cases V and XI) were macroscopically a single large cyst. Careful search

FIG. 5.—Photomicrograph Case 4. (See Fig. 4.) The benign form of adamantinoma. The tumor was composed chiefly of multiple small cysts. The cells are of the columnar type.

through the sections revealed stellate cells in all cases. The relative proportions of the types of cell varied within wide limits in the different specimens. Case IV was the most typical section. The stellate cells predominated while cuboidal cells were rare. In Cases I and III, the tumor was practically solid and composed of cuboidal cells having the characteristic appearance of squamous-cell carcinoma, although in certain sections the other forms of cells could be found. In Case IX the tumor was composed of cysts varying up to 2 cm. in diameter, but sections of the more solid portions closely resembled microscopically the so-called adeno-carcinoma of the parotid. Cases VII and XIV were somewhat similar.

Sex.—There were four males and eight females.

Age.—The ages at the time of onset varied from thirteen to seventy-three years. Six cases were between twenty and thirty when the tumor was first noticed, while six were over fifty. One form of this tumor is more commonly

noted in late life, but it is difficult to say that careful examination would not have demonstrated it at an early date.

Situation.—Upper jaw—three cases, lower jaw—nine cases. In the lower jaw, the disease usually arises in the body near the angle but any portion of the bone may be involved. When seen through the mouth the tumor appears as a bulging of the alveolar process, more marked on the external surface, often about a sound tooth. In the more advanced cases, the disease usually extends beyond the midline. In the upper jaw the tumors often invade the antrum but usually extend backward between the hard palate, which is absorbed, and the mucous membrane of the nasal cavity. In the three cases in which the upper jaw was involved, the tumors had extended beyond the midline in every instance.

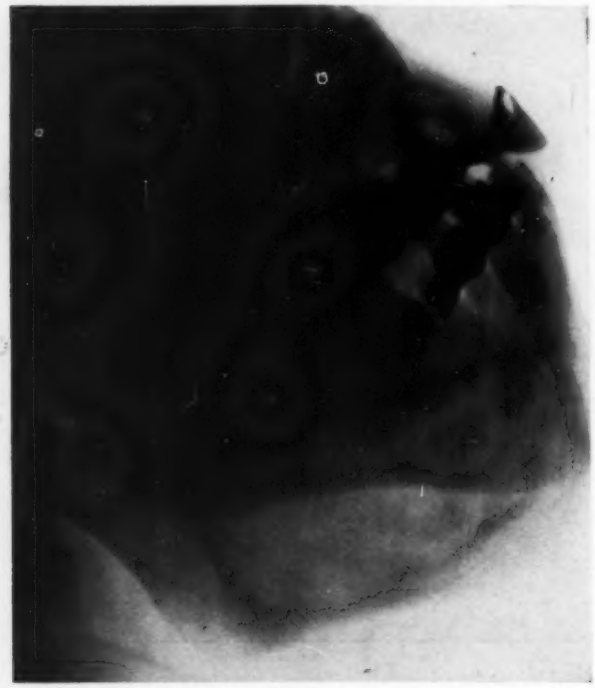

FIG. 6.—Case 5, female, thirty-three years of age. Tumor of seven years' duration. Curettage six years previous with immediate recurrence. X ray showing tumor of the body of the lower jaw extending forward from the angle. At operation there was one large cyst with some solid tissue in the posterior portion from which the diagnosis was made.

X-ray Examination.—The X-ray picture when the disease is situated in the lower jaw is usually characteristic. There is a central area of bone destruction and the appearance is that of a single large or many small cysts. Later when the growth has obtained considerable size, the bone may become entirely absorbed. These tumors are confused usually with benign giant-cell tumor or some other form of odontoma arising from the mesoblast elements, particularly the solid type often spoken of as central spindle-cell sarcoma, but the appearance of multiple cysts is characteristic. It is also at times confused with small dentigerous cysts or osteomyelitis. In the upper jaw the tumor extends to the antrum and the appearance is masked by the surrounding structure.

In all the cases in which the lower jaw was involved, the X-ray was typical. (Cases II, IV, V, VI, VII, VIII, XI, XIII and XIV. In Cases VI and VIII, the films were not available for review but there was a good description of the findings.

In the three cases in which the upper jaw was involved (Cases I, III and IX) it was possible to make the diagnosis from the X-ray in two cases only (Cases III and IX).

Symptoms.—There are no subjective symptoms characteristic of the disease. Objectively, there is a tumor of the jaw, centrally placed, with bone destruction and if the alveolus has been destroyed a fluctuating cystic area can usually be felt on the alveolar process or hard palate. In the more advanced cases there may be marked deformity, pathological fracture, and symptoms caused by pressure on adjacent structures or by secondary sepsis.

The diagnosis is made on the history of a tumor of long duration, and the X-ray. It is often impossible to make a definite diagnosis in an early case, but the probability of the growth being adamantinoma should be considered in all primary central cystic tumors of the jaw.

FIG. 7.—Case 2, female, thirty-seven years of age. Tumor of fifteen years' duration. Operated upon four times with recurrence. Metastatic glands present in the neck. Photograph of specimen. The multiple cystic condition can easily be seen. The coronoid process is occupied by a large cyst and has the appearance of being hypertrophied. To the right of this is seen the articular process. Glands of neck removed. Living without recurrence eight years later. (See Fig. 8.)

Contrary to the prevailing idea, the results of treatment of these cases as regards permanent cure by conservative operations were discouraging. Three cases (Cases I, III and XI) died of extension of the local growth and sepsis, two (Cases I and III) after two conservative operations, and one without treatment. The length of life in these cases from the onset of symptoms to death was seven years, one and one-half, and one year, respectively.

One case (Case VII) died of local recurrence and metastases in the glands of the neck and in the lungs fifteen years after the tumor was first noticed. Two operations had been performed on this case.

Seven cases (Cases II, IV, V, VI, VIII, XIII and XIV) had had from one to five operations performed, followed by a return of the disease and were living with local recurrence when seen by me from six to twenty-five years after the tumor was first noticed. Three of these cases have since had a radical operation performed; one, (Case II) had an excision of the lower jaw with dissection of the neck for metastatic glands and is well without evidence of disease eight years later. Two other cases (Cases XIII and XIV) had had excision of the lower jaw done one year ago and are living without disease at the present time. In the one case that had had radiation treatment (Case IX) excision of portions of both upper jaws was done fourteen months ago and there is no recurrence as yet.

In brief, ten cases had had conservative operations performed, and there was a recurrence in every instance. Of these, two cases (I and III) are dead from local extension of the disease and sepsis, and one, (Case VII) of metastases. Although obviously inadequate operations had been performed in many instances, in nearly every case one or more operations had been performed by competent surgeons who presumably removed all the visible tumor.

Bloodgood advises conservative operation but states that recurrence is common unless the operation is very thorough.

In light of these results the appropriate treatment would seem to be wide local excision, that is, resection of the jaw. Recurrences are to be expected after conservative operations, although these are usually local and the tumor in the average case is of very slow growth, the patient remaining apparently well for many years. Metastases are also more common than is generally supposed and the fact that the tumor is composed mainly of well-differentiated cells is no proof that it will not metastasize. On the other hand, a woman

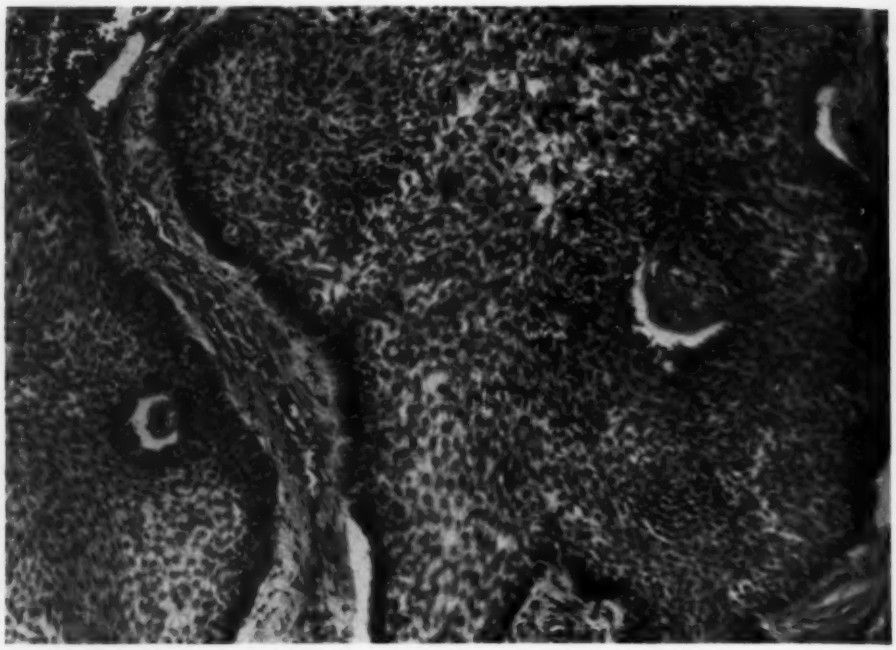

FIG. 8.—Photomicrograph Case 2. (See Fig. 7.) Section from the gland of the neck showing the tumor. A cellular form of adamantinoma composed chiefly of enameloblasts and columnar cells.

is very averse to the more or less mutilating operation of resection of a large portion of the lower jaw, and in young individuals with small tumors the conservative operation may be advised if the patient will agree to frequent examinations, and radical operation if there is recurrence. The prognosis in the individual case is difficult but I believe the more radical operation; that is, resection of the jaw, should be done if the cuboidal type of cell predominates in the tumor as this is probably the more malignant form of the growth, and it should also be done if the tumor is large. On the other hand, if the tumor is cystic and the prevailing cell on microscopic examination is the well-developed enameloblast, the probability is that the tumor is benign and any recurrence will be of slow growth and easily recognized. Case IV may be cited as an example of this type.

The deformity following resection of the upper jaw is comparatively slight. It is possible to fit a plate closing the defect in the hard palate, obviating the difficulty with phonation and mastication. Following the resection of the lower jaw, the deformity is greater but in certain instances a prosthetic apparatus can be fitted, while in others a bone graft may be inserted to fill in the defect.

ABSTRACT OF CASES

CASE I.—Male, fifty-three years. Tumor of left upper jaw of one year duration. Examination showed a tumor of the left upper alveolus from incisor to second molar. Patient operated upon and a large amount of tumor tissue removed. Radium inserted into cavity. There was slow recurrence and patient died of extension of the local disease six years later. Pathological examination showed a tumor containing numerous small cysts. In the first specimen removed the typical stellate enamel cells could be demonstrated, but the bulk of the tumor was composed of masses of cuboidal cells. A few cells of cylindrical type could be found in places. In a second specimen, removed three years later, no enamel cells could be found.

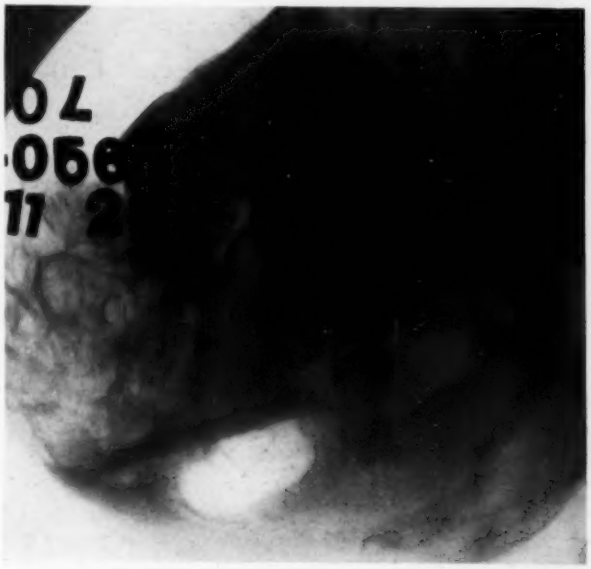

FIG. 9.—Case 13, male, thirty-one years of age. Tumor of lower jaw six years. Local excision three years ago with immediate recurrence. X-ray of lower jaw. The multiple cystic tumor can be seen near the symphysis. There are large cysts extending in the body to the angle on both sides. (See Fig. 10.)

CASE II.—Female, thirty-seven years. Tumor of the lower jaw of fifteen years' duration. Had been operated upon unsuccessfully four times. Examination showed a centrally situated cystic tumor in the left lower jaw, extending from the middle of the body to the articulation with bone destruction. Gland 4 cm. in diameter at the bifurcation of the carotid. Two-stage operation with radical neck dissection and later resection of one-half the lower jaw. Pathological report of both tumor of jaw, and gland showed cells typical of adamantinoma. All types of cells were seen but less differentiated forms predominated. Living without disease eight years later.

CASE III.—Female, seventy-three years. Tumor of left upper jaw four months. Had been incised. Examination showed multiple cystic tumor in the left upper jaw extending backward on the hard palate. X-ray showed increased density in the antrum. At operation an extensive tumor was found above the hard palate and below the nares extending into the antra on both sides. A large amount removed by morcellation and seeds of radium emanation inserted. Growth recurred in six months and did not yield to radiation therapy. Patient died about one year after operation. Pathological examination of the tumor showed solid masses of cells of cuboidal type which in places resembled cylindroma; a few areas presented the typical stellate cells of the enamel organ.

CASE IV.—Female, fifty-six years. Tumor of the right lower jaw for thirty years. Patient had had four previous operations, two of which had been extensive. Examination

showed a centrally placed tumor in the right lower jaw near the center of the body, with a pathological fracture of the jaw, compound into the mouth with resulting osteomyelitis. The jaw was resected and microscopic examination showed a tumor identical with that removed twenty-three years before. Columnar cells and stellate cells predominated.

CASE V.—Female, thirty-three years. Tumor of the right lower jaw removed seven years ago. This recurred one year later and has slowly increased in size. Right lower molars have been extracted. Examination showed a fluctuating cystic tumor in the alveolar process, occupying the posterior part of the ramus of the right lower jaw. X-ray showed bone destruction of the ramus of the jaw and the appearance of a multilocular cystic tumor. Operation—resection of portion of lower jaw containing tumor. Pathological examination—adamantinoma. Many large cysts and tumor cells, mostly columnar type, suggesting cylindroma. In places a few stellate cells.

CASE VI.—Female, thirty-eight years. Two years before admission tumor appeared near the symphysis of the lower jaw, extending to both sides of the midline. The teeth were extracted. Examination showed a medullary tumor at the symphysis. X-ray showed bone destruction and the appearance of multiple cysts. Operation advised, and anterior portion of lower jaw removed by surgeon in another city. Recurrence one year later. Pathological report only. Adamantinoma in which the columnar cells predominated, but portions of the growth showed typical stellate cells with many large cysts. When last heard from, two years after excision, there had been a recurrence of the growth. Further operation was advised.

CASE VII.—Male, thirty-seven years. Tumor of the right side lower jaw twelve years. Two incomplete operations. Glands removed from neck two weeks before admission, showed on pathological examination adamantinoma. Examination—a centrally placed cystic tumor occupying the lower jaw from the angle on one side to that on the other. Much deformity. Hard glands along anterior border of sternomastoid to the clavicle on both sides of the neck. No treatment. Three years later glands and tumor had both increased in size and there was evidence of lung metastases. Patient died one month later or fifteen years from the time the tumor was first noticed. Pathological report of tumor of jaw and gland showed same type of adamantinoma. There were many small cysts, the prickle and cuboidal cells predominated.

CASE VIII.—Female, forty-two years. Twelve years before examination tumor appeared in left lower jaw. This was of slow growth but had been much more rapid in past four years and had been incised and curetted a short time before admission to the hospital. Examination showed a centrally placed tumor in the left side of the lower jaw extending from the incisor tooth to the angle. In places this was fluctuant. X-ray showed a centrally placed tumor with bone destruction and the presence of multiple cysts. Operation—a portion of the jaw containing the cysts was excised. Pathological examination showed a multilocular cystic tumor with a small amount of solid tissue containing columnar cells and a few stellate cells. The appearance was typical of adamantinoma of the cylindroma type. Letter received from patient five years after operation stated that the growth had recurred. She refused further treatment.

CASE IX.—Female, sixty-eight years. Tumor of the upper jaw of six years duration. This had been previously treated by X-ray with some diminution in the rapidity of the growth at one time. Tumor had increased rapidly in size in the past year. Examination showed a cystic tumor 12 cm. in diameter in the upper jaw extending from the region of the first molar on the left to a similar position on the right. Both antra were involved, and the nasal cavity obliterated. Blood pressure 300. X-ray rather unsatisfactory but showed a multiple cystic tumor occupying both upper jaws. Operation—resection of the tumor with a greater part of both the upper jaws. Pathological examination—cystic tumor microscopically containing cells of cylindrical type characteristic of adamantinoma. In the greater portion of the tumor, the cells had an adenomatous arrangement,

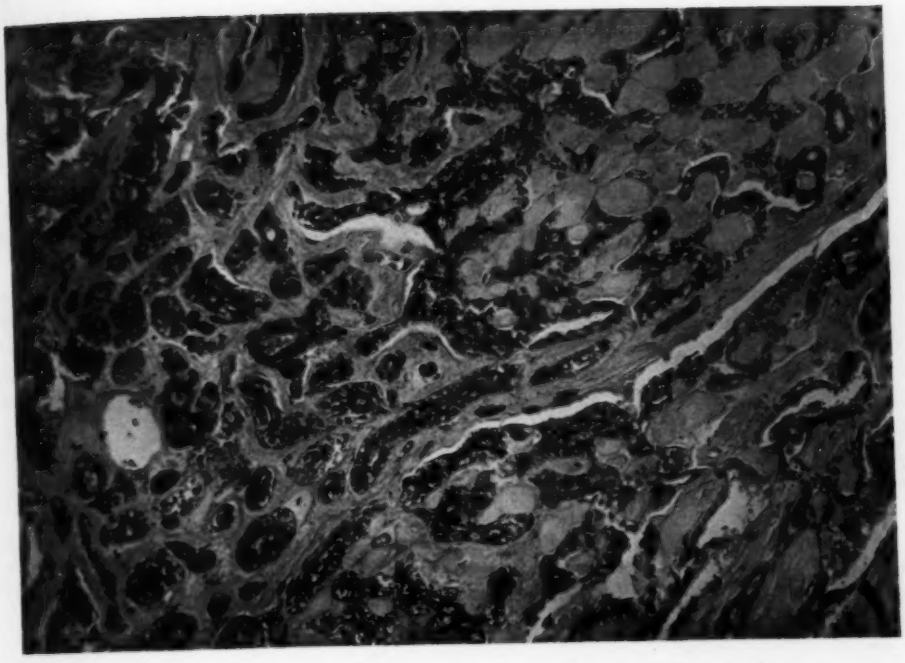

FIG. 10.—Photomicrograph Case 9. (See Fig. 11.) Tumor cells invading bone.

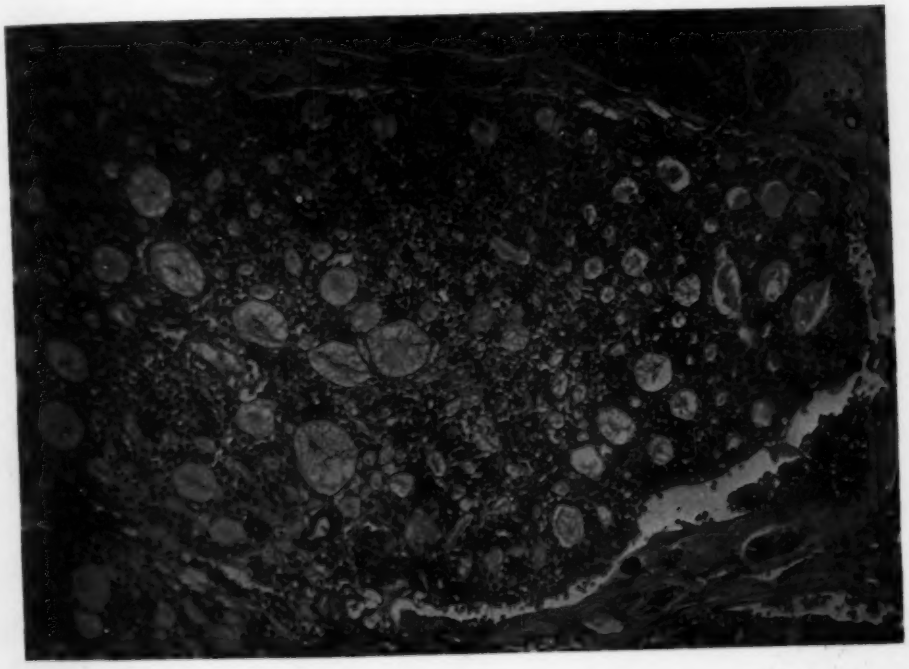

FIG. 11.—Photomicrograph Case 9. The adenomatous type of adamantinoma. (See Fig. 10.)

CASE X.—Male, sixty-five years. Tumor of right lower jaw for four years. One previous incomplete operation. Examination showed tumor of the right lower jaw near the angle, centrally placed and presenting multiple cysts. There was a gland 4 cm. in diameter hard, somewhat fixed at the bifurcation of the carotid. This patient had prostatic hypertrophy, myocarditis and bronchitis. He was not considered a suitable case for radical operation and, therefore, the diagnosis has not been confirmed by microscopic examination. One year later following X-ray treatment the gland in the neck was smaller but the tumor of the jaw showed no change.

CASE XI.—Male, sixty-two years. Tumor of the right lower jaw one year. Teeth had been extracted. Examination—at the region of the third lower right molar was a sinus extending into a cystic tumor of the jaw, centrally placed. X-ray showed central tumor apparently composed of multiple cysts situated just anterior to the angle of the jaw. Patient received no treatment and died nine months later. Pathological examination showed solid masses of the cuboidal type of cell.

CASE XII.—Male, fifty-two years. Tumor of the right upper jaw for twenty-five years. First consultation with a physician was ten years previous to his admission to the hospital. The tumor of the upper jaw had formed an abscess several times in the last two years. Examination showed a tumor of the right upper jaw situated external to the antrum and extending from the canine to the molar tooth. X-ray showed the typical appearance of an adamantinoma of the upper jaw. There were multiple cystic cavities destroying the bone. No operation was performed and the patient died twelve years after observation of intercurrent disease. The tumor of the jaw had changed but little during this time.

CASE XIII.—Male, thirty-one years. Colored. Tumor of lower jaw originating in the right body of six years duration. Growth excised without resection of the jaw three years ago. Examination showed a large tumor occupying the lower jaw and extending from the angle of the left to a similar position on the right. This was centrally placed and there were areas of fluctuation to be felt over the alveolar process. X-ray showed a multiple cystic tumor. Operation—excision of the entire lower jaw, the bone being divided anterior to the angles. Pathological examination showed the tumor to be chiefly cystic but in places the typical stellate and columnar cells of adamantinoma could be seen.

CASE XIV.—Female, fifty-eight years. Seven months before admission noticed tumor of the left lower jaw. Teeth were extracted shortly after by dentist on the diagnosis of alveolar abscess and osteomyelitis. Examination showed a smooth swelling occupying the left half of the lower jaw. X-ray showed the tumor composed of multiple cysts which were typical of adamantinoma. Operation—resection of the left half of the lower jaw from the symphisis to the angle. Pathological examination—adamantinoma, chiefly cystic. A few stellate cells but majority of the cells were of the cylindroma type.

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CANCER IN AND ABOUT THE MOUTH

A STUDY OF TWO HUNDRED AND ELEVEN CASES

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This survey was not undertaken as a basis for any broad conclusions, but rather to check our own work and results. We do not speak of cures, but believe that if we can add one year of healthful, comparatively comfortable activity to the life of a useful man we have made a real accomplishment.

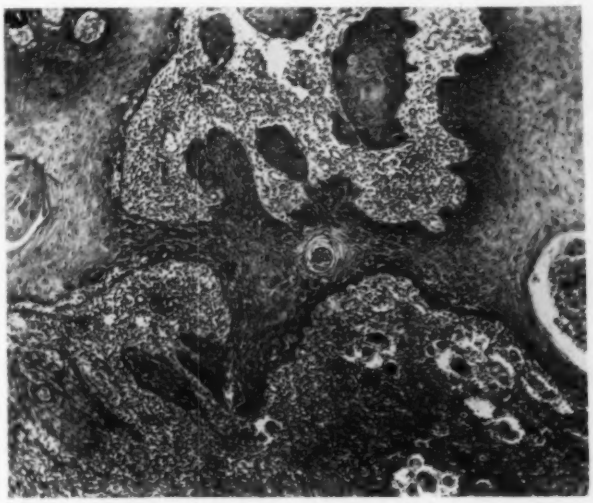

Fig. 1.—Case I.

If a patient dies as the result of a sincere attempt to eradicate cancer, it is a bad mark against surgery, but economically it is no disaster. If after complete relief from a mouth cancer, the patient is later carried off by a recurrence in some vital organ, he has had not only the benefit of the extra span of life, but has also been spared a much worse form of death, namely, from uncontrolled cancer of the mouth.

This presentation is facilitated by assuming the following growth sites, but these regional distinctions were noted chiefly because of their relation to treatment, plan of operative attack and prognosis.

Cancer does not love rules, but it has preferences of location which in turn seem to influence direction of growth and, to some extent, quality of malignancy. Extension will occur from one area to another, but the site of the primary appearance here defines the location. There seem to be some general tendencies as to the direction in which the extension will occur.

The anatomical locations are (1) buccal cavity mucosa, (2) lip, (3) tongue and floor of the mouth, (4) face, (5) pharynx and tonsil, (6) neck, and (7) accessory nasal sinuses and nasal passages.

(1) The *buccal cavity mucosa* group includes growths of the gums and palate, often classed as cancer of the jaw, a classification that we disregard

because the bone involvement is accidental and only incidentally influences the plan of attack.* Metastatic carcinoma of the jaw has been noted three times, once from the rectum and twice from the breast. This buccal cavity mucosa division also includes those growths which have originated from within, but have perforated the cheek.

(2) The true *lip* cancers arise from the exposed vermilion border. In this group are included those cases which came to us with healed lips, the result of operation, radiation or pastes, but with metastatic growths in the neck. These have been fairly frequent and there have been some patients

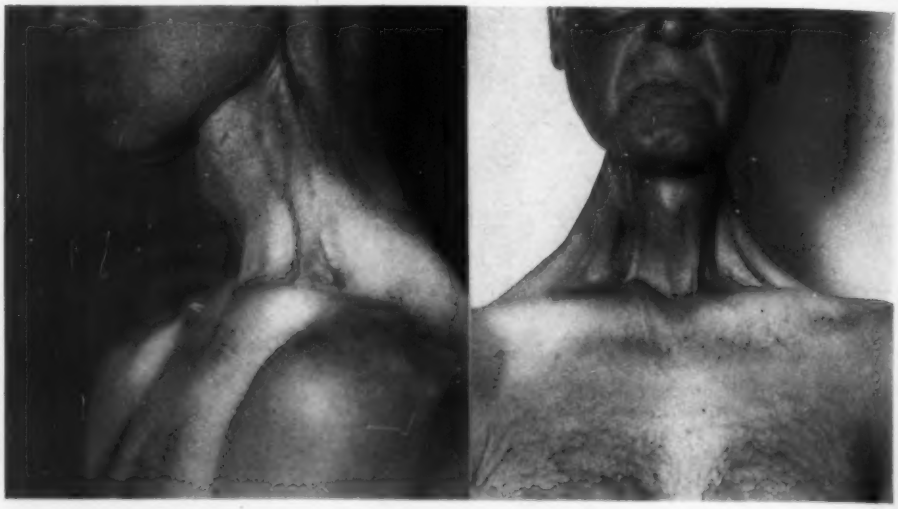

FIG. 2A.—Case II.

FIG. 2B.—Case II.

who, when questioned, at first failed to remember that they had had a sore on the lip treated years previous to the appearance of the growth in the neck.

(3) *Tongue,* both oral and pharyngeal parts, and *floor of the mouth.* Growths of the floor of the mouth are grouped with the tongue, both on account of the frequency of the double involvement and of the therapeutic indications. The floor of the mouth is less frequently involved from the gums than from the tongue; and further, a growth on the gum is usually destroyed with a soldering iron, while the tissues of the involved floor of the mouth or tongue demand deep removal or radiation. From the tongue, a growth may extend widely into the cheek, fauces or pharynx, usually invading these tissues behind the alveolar process.

(4) *Face,* squamous-cell carcinomata arising from the skin, not including growths perforating from the deep structures.

(5) *Pharynx and tonsil,* growths arising in the oral pharynx.

(6) *Neck,* including tumors arising deep in the neck in patients in whom no primary site could be found. Treves pointed out the possibility of pri-

* The paradental epithelial cell remnants (paradental débris of Malassez) may possibly be the starting point of some malignant growths but we have found no definite evidence on this point.

mary neck growths arising from epithelial remnants, but our observations are leading us to an increasingly strong belief that the majority of them are metastatic from unrecognized growths in the upper alimentary or respiratory tracts.

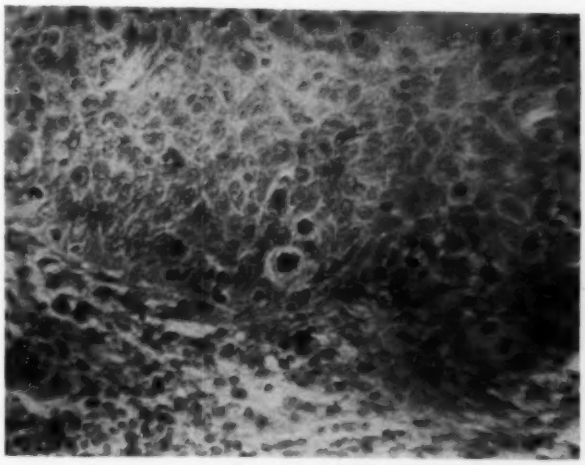

FIG. 2C.—Case II.

(7) *Accessory nasal sinuses and nasal passages,* together with the naso-pharynx.

We have also found it convenient to distinguish four arbitrary stages of growth as noted at the first examination. (1) *Early:* Growths of relatively short duration and where there is no gross evidence of glandular involvement. These are frequently small enough for apparently complete excision for the biopsy. There were only ten in this stage out of a total of two hundred and eleven cases. (2) *Medium:* More active growths, still not of great size nor involving tissues difficult to eradicate. Many of these patients have enlarged regional glands. Stages 1 and 2 are regarded as belonging to the likely curable class. There were thirty-five in this stage. (3) *Advanced:* This stage includes growths which from their size or from the tissues involved render the treatment more hazardous and the prognosis distinctly less promising. There were one hundred and seventeen in this stage. (4) *Inoperable:* Growths too far advanced for any prolonged relief to be expected, regardless of the type of treatment. A few are included in this stage because of physical disability, aside from the carcinoma. Radiation in some form was used on most of these patients. There were forty-nine in this stage.

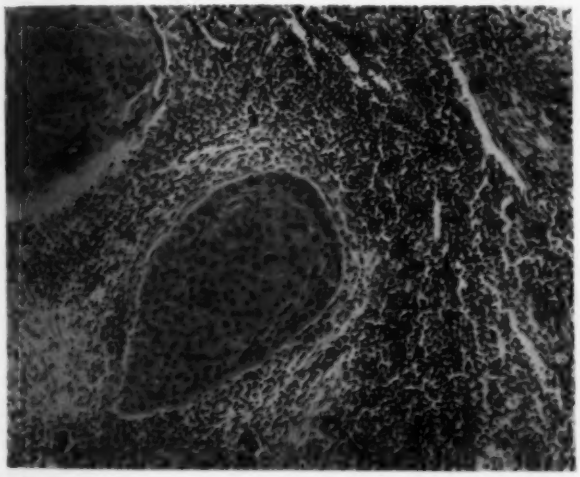

FIG. 2D.—Case II.

Although there can be no fixed lines demarcating any two stages, this classification has proved of practical use, as it gives a basis for prognosis

from clinical findings. The size, the duration, the rate of growth, the histology and the condition of the patient are all given consideration in summing up the prognosis and in planning treatment. No one criterion has been found to offer a basis of prognosis accurate enough to present a percentage plan to the patient of his chances of life.

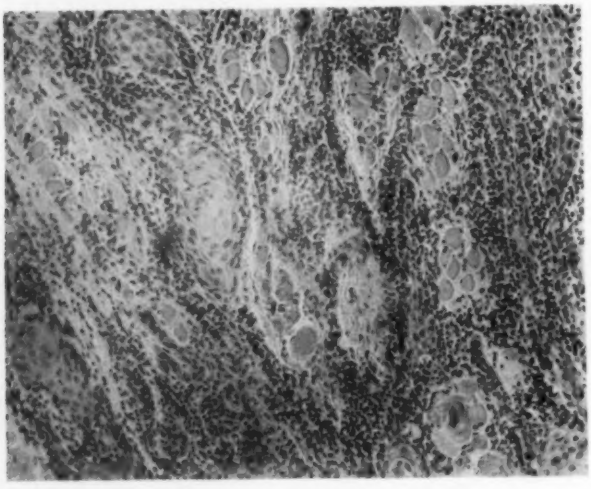

FIG. 3A.—Case III.

Some of the advanced and inoperable cases have not had biopsies; and in a few others, the microscopic sections were not available. An attempt has been made to grade these growths according to Broder's classification (Figures 13, 14, 15 and 16). In some cases several slides have been studied; the ones from the biopsy, those from the specimen at the operation and those from the regional glands. In some of the earlier cases, biopsy was rather avoided for fear of spreading the disease, but we now feel strongly that there are advantages in the pre-treatment microscopic study that outweigh the dangers. By the total removal of small growths, or by the use of the cutting cautery for biopsy combined with radiation, the dangers of implantation must be materially reduced.

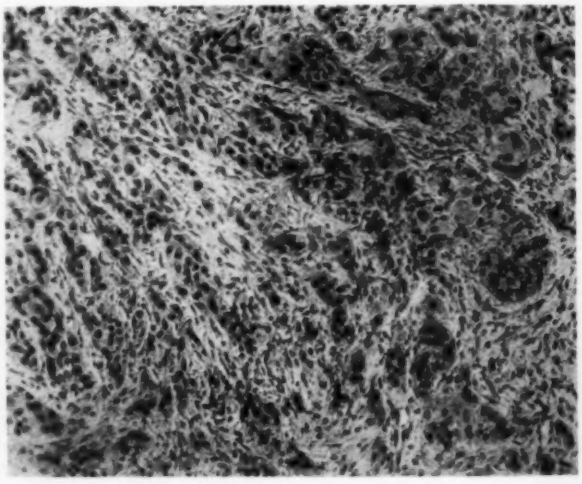

FIG. 3B.—Case III.

Throughout this series, an attempt has been made to correlate histology with the other factors, taking into account cellular differentiation, mitoses and the distribution of the cancer cells; but individual ideas influence microscopic grading perhaps much as they do in determining clinical stages. While it may be claimed that one cell or a small group of cells may prove malignancy, various stages of differentiation may often be demonstrated in a single section. This necessitates a fairly thorough examina-

tion and final balance of the differentiated and undifferentiated cells in determining the group. In spite of these uncertainties, it would appear quite certain that there is a definite relationship between the stage of cellular differentiation and the virulence of the individual growth. Therefore, this latter has a bearing on prognosis and on the character and extent of the treatment.

Our clinical observations over a much larger series have led to the rather definite conclusion that many growths are for a time held in relative abeyance,

TABLE I.

Stage	Early				Medium				Advanced				Inoperable			
Grade.....	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
Buc. cav.				2	7	2	1	1	4	17	7	7		2		4
Lip.....		2	1		3	3			3	3	4	7				2
Tongue..	1			1		2	2	2	1	6	9	7		1		1
Face.....	1				1	1		1	2	1	1	4				1
Pharynx.									1	1	2	2				5
Neck....							1			1		4				4
Antrum..								1				6		1		1
	2	2	1	3	11	8	4	5	11	29	23	37		4		18

Total graded—158: Grade I —24
Grade II —43
Grade III—28
Grade IV—63

Stage	Early	Medium	Advanced	Inoperable
Buc. cav.	2	16	41	17
Lip	3	6	20	6
Tongue	3	7	25	7
Face	2	4	11	1
Pharynx			8	6
Neck		1	5	8
Antrum		1	7	2
	10	35	117	49

Total—211

but later take on much more rapid growth, if not a real increase in malignancy. The opportunities to make early and late microscopic examinations on the same growth are relatively rare, but this series shows a higher percentage of growths of Grades 3 and 4 in the advanced and inoperable cases than in the early and medium cases. In drawing this conclusion, changes of only one degree were not considered of worthy note (Table I).

We have observed a type of growth that occurs in the mouth that very closely resembles cancer in its clinical progress and its outcome, but in which repeated microscopic examinations do not show the typical breaking through of the epithelial cells, which is considered necessary in the definition of cancer. These might rightly be considered as a precancerous stage, and in several

a breaking through of the cells has been demonstrated in a very small area of a relatively large growth. However, several have grown for long periods of time, have attained large size and have accomplished great destruction without any breaking-through being demonstrated. (Case I.)

When carcinoma could be demonstrated in the glands, the degree of malignancy nearly always approximated that of the primary growth. The glands were graded one grade lower seven times, one grade higher four

TABLE II.

The grade of the metastatic growth rather closely followed that of the primary tumor.
Of 114 gland examinations, 65 were found to be carcinomatous.
Of 65 glands with positive carcinoma, 60 were graded.
Of the 60 graded metastases:

7 were Grade I	— Of these:	6 came from Grade I primary growths;
		1 from a Grade II growth.
9 were Grade II	— Of these:	7 came from Grade II primary growths;
		2 from Grade III growths.
14 were Grade III	— Of these:	1 came from an ungraded primary growth;
		1 from a Grade II growth;
		8 from Grade III growths;
		4 from Grade IV growths.
30 were Grade IV	— Of these:	8 came from ungraded primary growths;
		1 from a Grade II growth;
		3 from Grade III growths;
		18 from Grade IV growths.

1 undifferentiated growth in a lymph-node came from a primary adeno-carcinoma of the tongue.

4 were not graded — 2 from ungraded growths;
2 from Grade II growths.

In 49 glands, no carcinoma was found. Of these:

1 was from an adeno-carcinoma of the cheek;
7 were from ungraded growths;
9 were from Grade I growths;
15 were from Grade II growths;
8 were from Grade III growths;
9 were from Grade IV growths.

times, and two grades higher one time. Glandular metastases appearing long after the apparent eradication of the primary growth were practically always of the third or fourth grades; and, where the data was available, were found to have come from growths of original high malignancy. No malignancy was found in forty-nine out of one hundred and thirteen gland examinations; but this does not necessarily mean that these glands were not affected. When cancer was microscopically demonstrated in the glands, there were seven Grade 1, nine Grade 2, fourteen Grade 3, and thirty Grade 4. Of five that were not graded, one was a very malignant adeno-carcinoma from the only adeno-carcinoma of the tongue in the series. (Table II.)

In most cases, the glands were removed by radical block dissection. The failure to demonstrate metastases microscopically does not mean necessarily that there was no glandular involvement. Results are, of course, better in the group where no carcinoma was demonstrated, but there are cases in the series which show that undifferentiated carcinoma, even affecting the glands

TABLE III.

Longevity Relative to Lymph-node Infection.

Grades	No carcinoma	I	II	III	IV
Alive 1–5 years	17	2	2	2	5
Alive 5–12 years	10		1	5	1
Post-operative deaths	6	2	1	4	7
Treated cases, dead later	8	2	3	1	5*
Treated cases not traced	7	1	2	2	1
	48	7	9	14	19

* One suicide.

of the neck, is not an absolutely hopeless situation. However, these cases call for the most extensive removal. See Cases II and X. There were seven Grade 3 cases that had glandular metastases still alive three, four, seven, seven, eight, eleven and twelve years after treatment; six Grade 4 after one, one, two, three and a half, four and seven years; and one Grade 4 case that

TABLE IV.

Longevity Relative to Stage and Grade of Primary Growths.

	Stage			Grade			
	Early	Medium	Advanced	I	II	III	IV
Alive 1–5 years	2	12	23	8	8	6	8
Alive 5–12 years	3	9	8	4	7	5	1
Post-operative deaths	1		28	3	3	8	11
Treated cases, dead later	1 suicide		32	4	8	6	13*
Treated cases not traced	3	8	11	5	8	2	6
	9	29	103	24	34	27	39
Per cent. cured or well	66	72.4	32†	50	43	40.7	23

* Eight refused treatment or went elsewhere for it.
† Forty-three per cent. if the post-operative deaths are not counted.
Twelve more patients have been added to the 1–5 year group since this table was made.

lived three years before a recurrence. (See Cases II, III, IV, V, VI, VII, VIII and IX. Tables III and IV.)

The results of treatment can best be shown in tabulations. There is a very high operative mortality, an average of 21.5 per cent. according to the number of patients. In this series, one hundred and eighty-nine major operations were done on one hundred and thirty patients. All but one of the

post-operative deaths occurred in advanced cases where very radical operations were done, and the growths in nearly all of the cases were poorly differentiated ones. It seems that the farther back in the mouth and pharynx the operation is carried, the higher the mortality. This may be due in part to the increased inability to get rid of mouth secretions, either externally or by swallowing, which predisposes to respiratory infection. Stamina on the part of the patient and constant efficient attention by the nurse do make for better results. Some patients fail to give any help of themselves. When tracheal tubes are in place, expulsive coughing occasionally through the day will do more to clean out the trachea and bronchi than anything else; but it has been impossible in some instances to keep the airway clean by any means, including suction. Radiation to temporarily stop the salivary flow has been considered, but not tried so far; because, in spite of the annoyance of it, it often seems to be the one thing that keeps the total secretion movable so that it can be gotten rid of. Death occurred nineteen times from pulmonary complications, three times from cardiac complications, three times from hemorrhage. Of four cases in which the common or internal carotid artery was tied, four died. Two of these, however, apparently died of pneumonia. (Table V.)

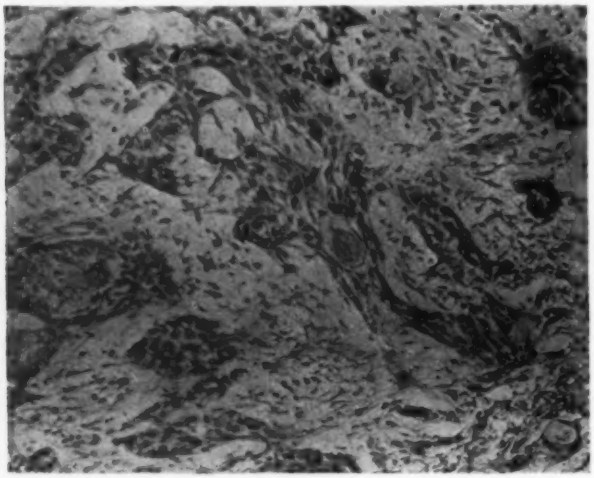

FIG. 4A.—Case IV.

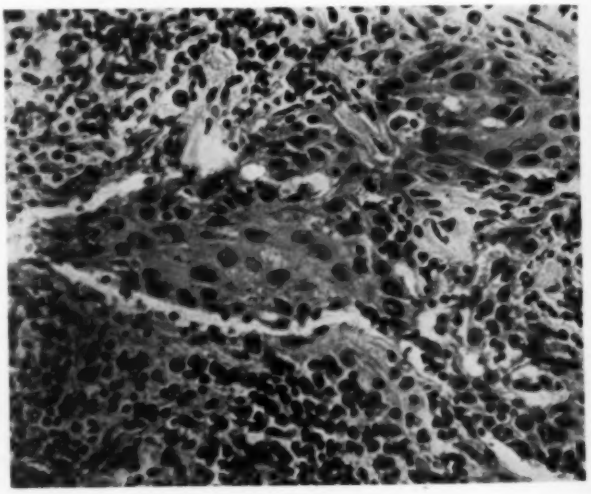

FIG. 4B.—Case IV.

Of the treated early cases, 66 per cent. are supposed to be cured. Of the treated medium cases, 72.4 per cent. are alive; and of the treated advanced cases, 32 per cent. are known to be alive and without known recurrence. Of

those advanced cases that survived operation, the percentage still alive is 43 per cent.†

The percentages of living patients without known recurrence, with growths of Grades 1, 2, 3 and 4, are 50 per cent., 43 per cent., 40.7 per cent. and 23 per cent. respectively. Untreated cases do not figure in these percentages, but those lost track of are counted. No reports could be obtained on forty-

TABLE V.

Post-operative deaths	29
Stage of growth	28 advanced
	1 early
Grades: Grade I	3 cases
Grade II	3 cases
Grade III	8 cases
Grade IV	11 cases
Ungraded	4 cases

Cause of death:

Pulmonary complications	19
Cardiac complications	3
Secondary hemorrhage	3
Common or internal carotid ligation (2 from pneumonia)	4

Death occurred from 1 to 42 days after operation.
Average time of death—10½ days after operation.

	Total cases	Radical operations	Neck diss.	P.-oper. deaths		Total no. oper. at separ. times
				Number	Per cent.	
Buccal cavity	76	53	44	14	26.5	76
Lip	35	22	21	2	9	31
Tongue	44	26	23	7	26.9	42
Face	18	12	4			14
Pharynx	14	8	6	3	37	10
Neck	14	6		2	33	6
Antrum	10	8	1	1	12.5	10
	211	135	99	29	21.5 (Average p.-oper. death rate)	189*

* The post-operative death rate according to the number of operations is, of course lower than that according to the number of patients.

one patients. Of these, twenty-eight are probably dead and thirteen are possibly alive.

There are seventy known deaths other than the post-operative ones. Of these, thirty-four had been treated by operation and radiation and thirteen by radiation; sixteen refused treatment or were sent home for radiation, seven were untreated. Subsequent death from cancer is recorded in twelve or fifteen cases. All but three of these cases were advanced or inoperable,

† Most of the late reports on the patients have been obtained by the Social Worker on the Surgical Service.

and there were four Grade 1 growths, ten Grade 2, seven Grade 3, and twenty-one Grade 4.

CASE I.—Male, fifty-nine, white. Three years before admission, the patient's lips became painful and reddened, and he noted a lump in his cheek. One year ago, lips and growth on right cheek became worse. He was given elsewhere four radium treatments and "electric destruction" three times.

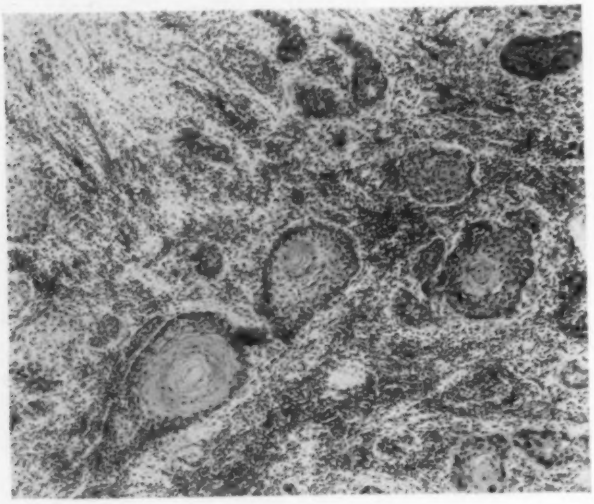

FIG. 5A.—Case V.

Upon admission, the epithelium of the lip was found to be reddened, thinned-out, cracked and painful. There was a widespread, smooth leukoplakia over the right cheek as far back as the molar region. In the molar region, there was a papillomatous ulcer one and one-half centimetres in diameter. The edges were firm and everted, but not as hard as is usually seen in cancer. The process extended into the upper fornix and because of thickening and an abscess deep in the cheek, the mouth could not be opened over one and one-half centimetres. On the outside, there was a dome-shaped induration over the centre of the cheek with a small opening draining pus from deep within the cheek.

The specimen removed showed a verrucous growth one and one-half centimetres in diameter. The borders were fairly well demarcated, but were found to extend down into the ulcerated area in the cheek. The microscopic picture resembled a benign papillomatous growth rather than a true cancer, as may be seen in the microphotograph. It was because of this picture that three biopsies were done before radical operation was instituted. (Figure 1.)

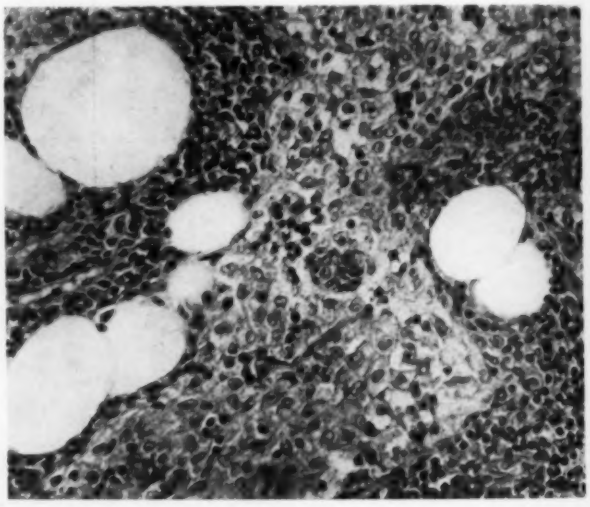

FIG. 5B.—Case V.

CASE II.—Male, forty-six, white. The patient noticed a small tumor in the floor of the mouth three months before his admission to the hospital. He had received no treatment.

Examination showed a smooth, flat ulcer in the left side of the floor of the mouth, not more than one centimetre in diameter. No enlarged regional lymph-nodes were felt. Without previous biopsy, because we had learned to regard this clinical picture as denoting high grade malignancy, an excision of half of the tongue was done, followed four months later by a left neck dis-

section. Two years later a right neck dissection was done, on account of recurrence on this side. The photographs were taken seven years after the first operation, and show the extremely radical neck dissections that are done on these cases. (Figure 2, A and B.)

Pathology.—The type of growth this tumor illustrated may be seen in Figure 2 C. The cancer cells are very poorly differentiated and mitoses are abundant. The primary growth has been given a Group 4 grading. In Figure 2 D, taken from one of the regional glands, there are two areas distended with cancer cells and surrounded by adenoid tissue. Mitoses are not as frequent as in the initial lesion, but even here differentiation is not especially good. From a study of this and other areas, the gland metastases have been given a Group 3 grading.

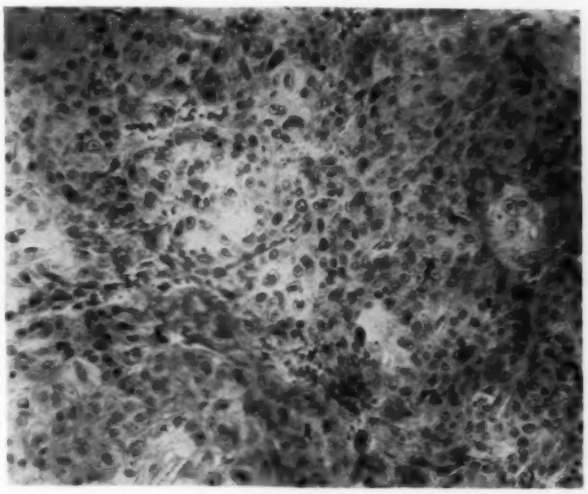

FIG. 6.—Case VI.

CASE III.—Male, fifty-one, white. One year before the patient was seen, he noticed a blister at the muco-cutaneous border of the right lower lip near the angle. Four months later a mass appeared beneath the right jaw.

Examination showed an ulcer at the corner of the right lower lip 2 x 1 centimetres. The ulcer was shallow, with a dry, gray base and with hard everted edges. A right submaxillary lymph-node was very large, hard and movable.

A right neck dissection was done, with a large V-shaped excision of the ulcer. The patient is well now, eleven years after the operation.

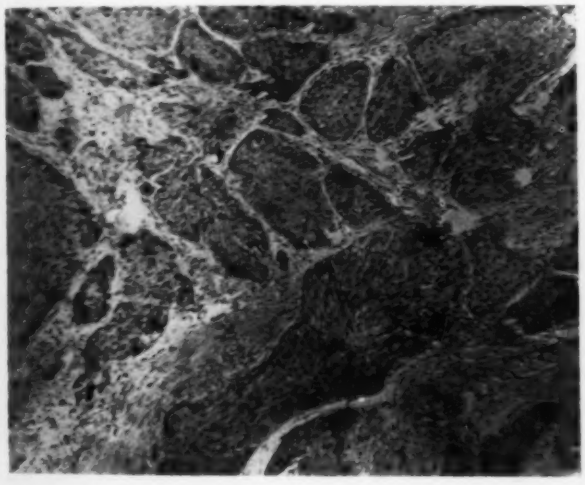

FIG. 7.—Case VII.

Pathology.—Figure 3 A is taken from the primary growth. There is abundant keratinization present. The marked inflammatory reaction present is perhaps due to the proximity of the ulcer, Grade 3. Figure 3 B is from one of the regional lymph glands. The normal architecture of the gland has given way to the extensive carcinomatous proliferation. Differentiation is not as complete as in the primary lesion. There is practically no hyalinization and numerous mitoses may be seen. Fairly extensive fibrous tissue proliferation is present. This gland has been graded 3.

CASE IV.—Male, fifty-six, white. Three and a half years before admission into the hospital, the patient noted a small ulcer beneath the tip of the tongue. This was excised locally and was said to have been diagnosed microscopically as a benign lesion There

was a recurrence within two months. For the last nine months before admission, there had been considerable bleeding and pain.

Examination showed a large ulcer involving the entire under-surface of the tongue and a portion of the floor of the mouth on the right side. The edges were hard, everted, tender and bled easily upon manipulation. There was a mass in the upper left part of the neck fixed to the jaw.

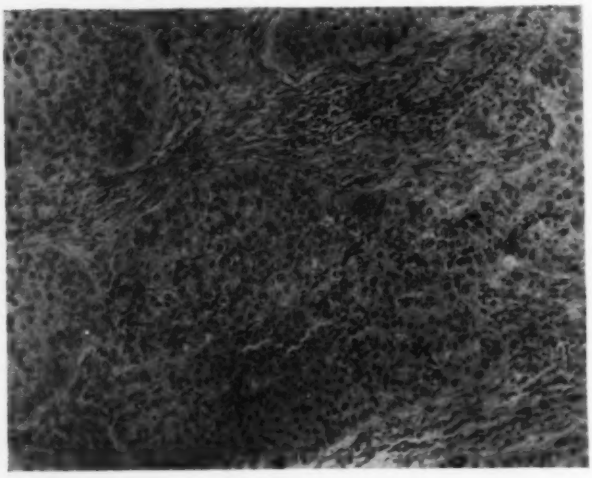

FIG. 8.—Case VIII.

Following a low tracheotomy, there was simultaneous bilateral upper neck dissection and removal of the tongue and floor of the mouth, and deep cauterization of the body of the mandible.

Seven years later, a new focus developed in the larynx that apparently was unrelated to the previous growth. In spite of treatment, the process extended deep in the neck.

Pathology.—In Figure 4 A, very little hyalinization is seen. In spite of the spindle shape of the cells seen in this area, this tumor has been given a Grade 3. Other areas from the tumor showed even poorer differentiation with marked invasive properties. Figure 4 B shows an early metastasis to a regional lymph gland. The clear cancer cells may be seen surrounded by fairly normal lymphoid tissue.

CASE V.—Male, forty-eight, white. The patient had noticed a lump on the tongue five years previously which was then excised. He sought treatment for a recent recurrence.

Examination upon admission showed a hard, red, ulcerated area involving most of the upper surface of the tongue. The edges were everted and showed a tendency to bleed. The tongue was hard, swollen and tender. There were palpable glands in both submaxillary triangles.

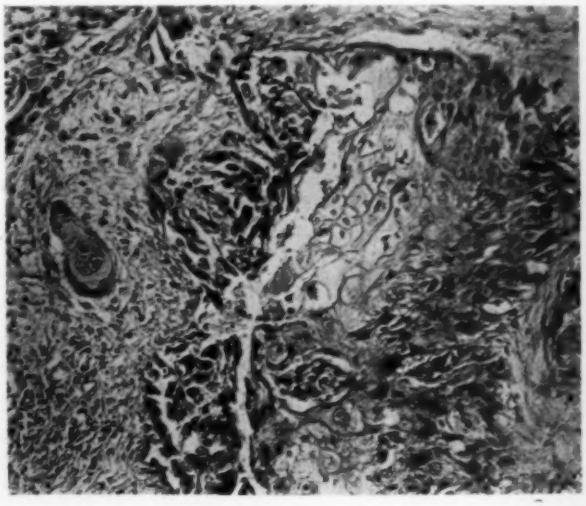

FIG. 9.—Case IX.

A tracheotomy was done followed by a complete removal of the tongue with an upper neck dissection on both sides. The patient returned at later dates for lower neck dissections on both sides, and for excision of a small nodule just above the clavicle that proved to be inflammatory in origin. The patient is well now and able to continue his profession as a physician twelve years after the operation.

Pathology.—Figure 5 A, from the primary growth, shows good differentiation of the carcinoma with tendency toward pearl formation. There is a widespread

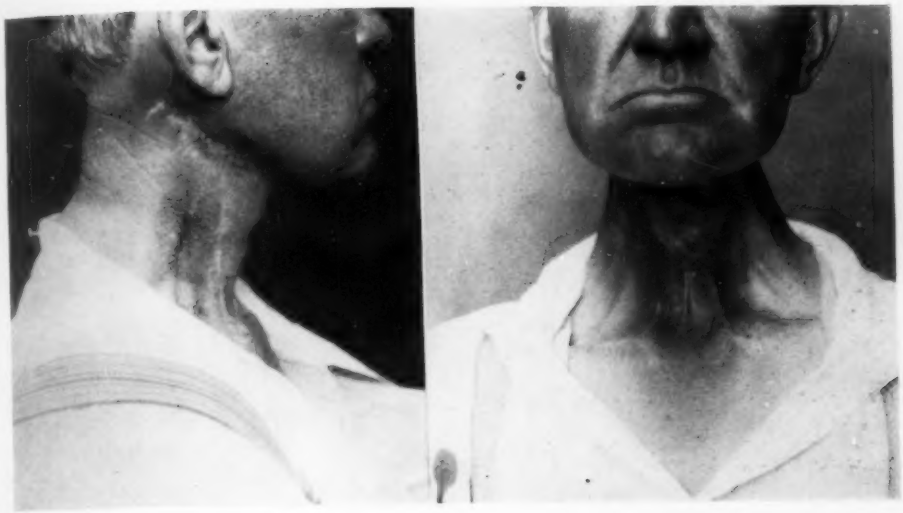

FIG. 10A.—Case X.

FIG. 10B.—Case X.

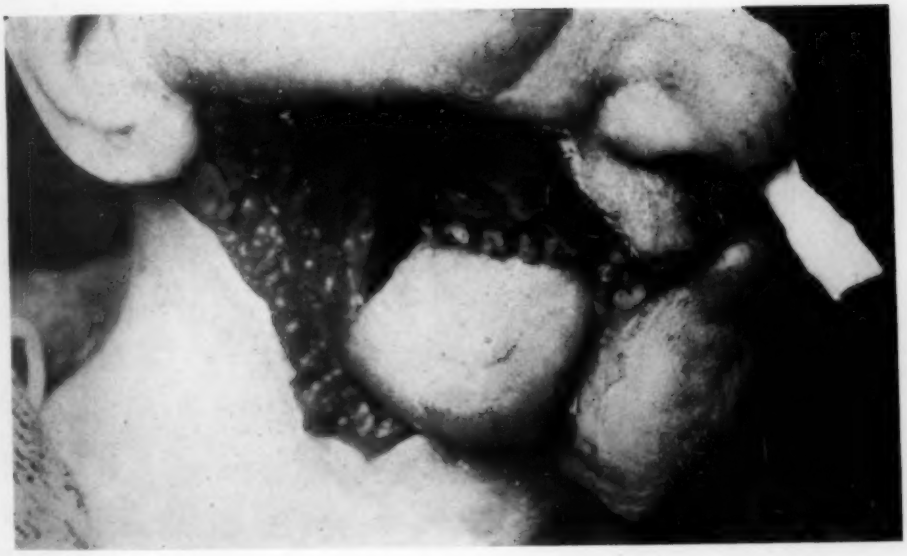

FIG. 11A.—Case XI.

inflammatory reaction due, no doubt, to the proximity of the area seen here to the ulcer. Grade 2.

Figure 5 B shows early invasion of a regional lymph-node. Differentiation is not quite so good as in the primary lesion. The large pale cancer cells may be seen surrounded by adenoid tissue containing dilated lymph spaces. Grade. 3.

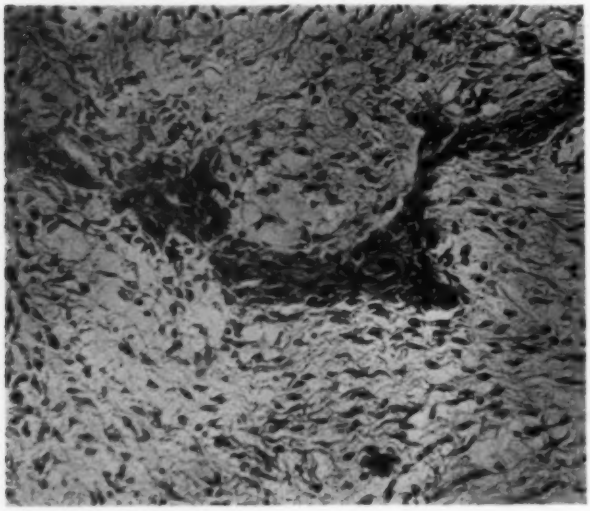

FIG. 11B.—Case XI.

CASE VI.—Male, fifty-five, white. One year before this patient entered the hospital, he noticed a small area beneath the right ear that became scaly, increased in size and ulcerated. Plasters were applied. The mass continued to grow.

Examination showed a cauliflower ulcer below and involving the lobe of the right ear. The ulcer was three centimetres in diameter, and its base was formed by the mastoid bone and the sterno-mastoid bone and the sterno-mastoid muscle.

dissection of the upper part of the right neck, including the parotid gland.

Pathology.—Figure 6. Differentiation is poor. There is considerable anaplasia present. Mitoses may be seen. Cell outline is in many places indistinct, giving the appearance of a syncytial arrangement. Grade 4. This patient has had no recurrence following the primary excision of the tumor, four years ago.

CASE VII.—Male, forty-five, white. Onset one year before admission, with hard, painless nodule back of ear. This soon ulcerated. Several plasters were applied. The growth increased rapidly in size. X-ray therapy was given. Since then, there has been considerable pain.

Upon examination, an oval ulcer 2½ x 2 centimetres was noted back of the left ear with a rolled, hard border and about five millimetres in depth. There were palpable lymph-nodes on both sides of the neck. There was a generalized hyperkeratosis of the skin.

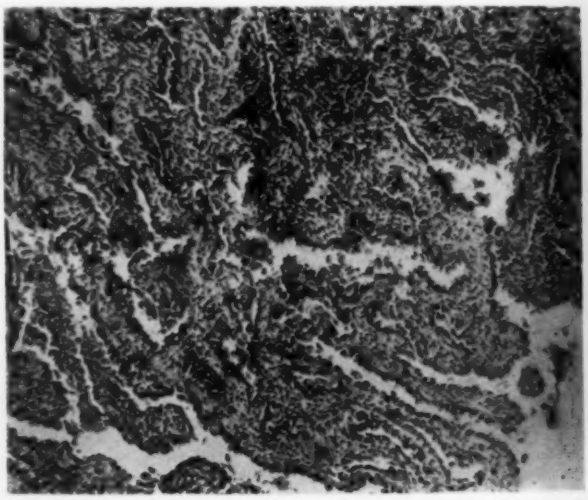

FIG. 12A.—Case XII.

The patient had a complete left neck dissection with removal of the parotid gland, and is well now three and a half years after the operation.

Pathology.—Figure 7. There are masses of carcinoma cells surrounded by a dense

fibrous tissue stroma. Here and there spindle cells may be seen, but from a study of the section as a whole this tissue has been given a Grade 3. Sections from the glandular metastases not shown here present approximately the same picture.

CASE VIII.—Male, sixty-four, white. Fourteen months before this patient was seen by us, he noticed that his throat was becoming sore and that the tonsil on the right side was red. He had received no treatment.

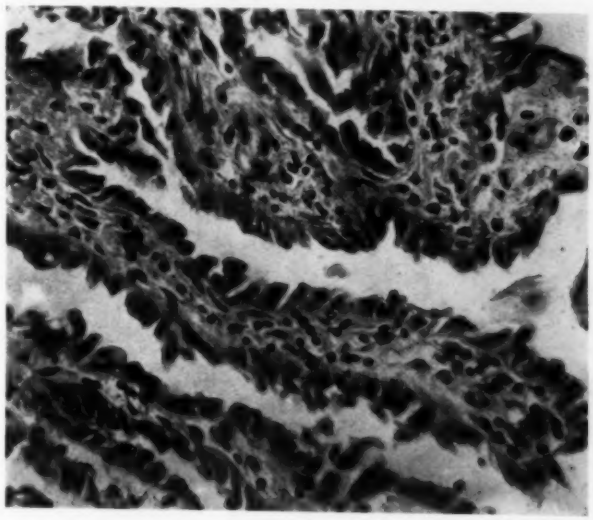

FIG. 12B.—Case XII.

Upon admission to the hospital, the right tonsil and anterior pillar were found to be almost completely destroyed by a dirty ulcer extending up to the hard palate. There was an enlarged gland in the anterior triangle of the right side of the neck.

Radium therapy was followed by a complete neck dissection on the right side. Several weeks later, following a tracheotomy, a radical excision of the tumor was done along with excision of one-half of the tongue. This was followed by further radium therapy. He is well now, seven years after the first operation.

Pathology.—Figure 8. In spite of very definite cellular outline, there is no prickling or hyalinization. In other areas, the resemblance to squamous cancer is still less. Very little stroma is present. This cancer has been given a Grade 4.

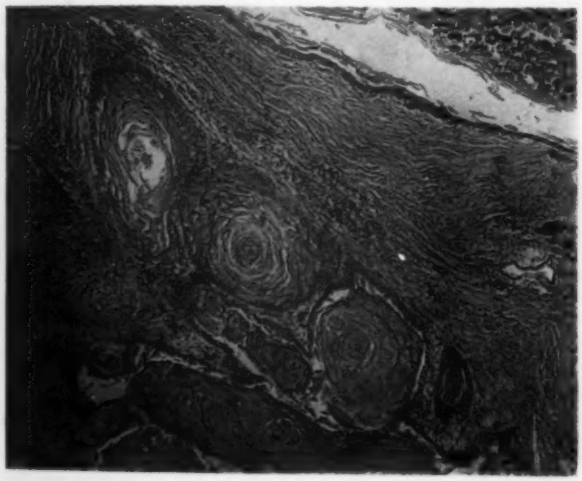

FIG. 13.—The section shows epithelial proliferation in a fairly dense fibrous area. Pearl formation is present and cell differentiation is complete enough to group this tumor as a Grade 1.

CASE IX.—Male, fifty-six, white. The patient noticed a mass in the posterior triangle of the neck on the left side and a mass in the tonsillar region two months before admission into the hospital. It grew very rapidly.

Examination showed the left anterior pillar and tonsil to be involved in an ulcer 2 x 2 centimetres, extending down to the alveolar ridge and completely destroying the tonsil. The mass was hard and not especially tender. There was a mass behind the ramus of the left jaw, apparently continuous with the mass in the pharynx. An enlarged lymph gland was felt at the angle of the left mandible.

A complete lower neck dissection was done on both sides followed by removal of

the tongue, the floor of the mouth and the upper lymphatics at a later date. The patient died eight years later of lobar pneumonia, without further evidence of carcinoma.

Pathology.—Figure 9. This section has been taken through one of the regional lymph glands, the normal architecture of which has been greatly distorted. In spite of the fact that no epithelial pearls were seen and no prickling, the flattening out of the cells and hyalinization has given it a Grade 2.

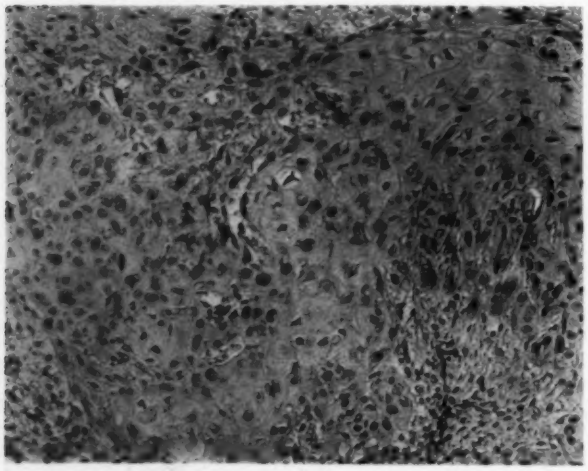

FIG. 14.—The cells are flattened and show a fair amount of hyalinization. However, there is considerable variation in the size and shape of the cells. Some mitoses are present. This carcinoma has been given a Grade 2. It probably should be more properly considered in a grade between Grades 1 and 2.

CASE X.—Male, fifty-five, white. The patient noted a small papule on the tongue two years before admission. He consulted a physician who gave him radium treatment. Later, a mass appeared in the neck.

Examination showed an ulcer 2½ x 1½ centimetres in diameter with hard, raised edges occupying the position of the vallate papillæ and going backward for attachment to the posterior faucial pillar of the right side. There was one large lymph-node at the bifurcation of the carotid on the right side.

A preliminary tracheotomy was done followed two weeks later by complete excision of the tongue with an upper neck dissection on both sides. Later, a lower right neck dissection was done. Several weeks after this, a lower left neck dissection was performed. Figure 10 A and B, taken three years after the operation, show the neck following the block dissections. Both internal jugulars and sterno-mastoid muscles are absent. The patient has a fair voice and is making his own way. The carcinoma was of low Grade 1 malignancy.

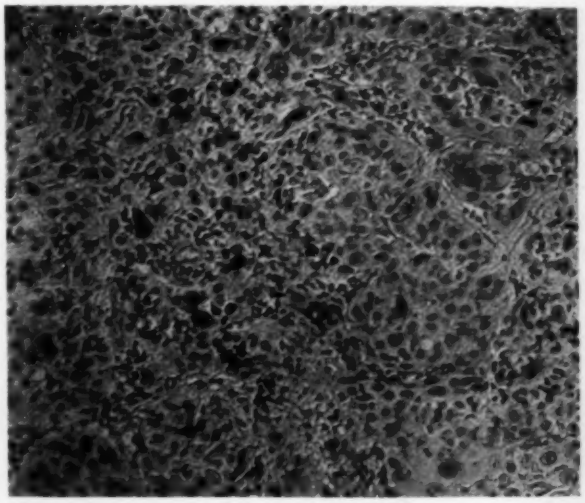

FIG. 15.—There is very little keratinization. There is a marked variation in the size and shape of the cells. Mitoses are easily demonstrated and giant-cell formation may be seen. There is very little fibrosis present. The poor differentiation has placed this carcinoma in Grade 3.

CASE XI.—Male, forty-eight, white. About two years before admission to the hospital, the patient noted a small ulcer on the mucous membrane of the right cheek in the molar region. He used caustics locally without improvement and later consulted a physician. He was given two radium applications followed by a local excision of the ulcer two months later. There was a recurrence

which was removed with the actual cautery. Following this he had four X-ray treatments.

Upon admission to the hospital, a hard ulcer was found in the right cheek opposite the molar region with induration extending down to the mandible. The ulcer crater was 2 centimetres in diameter. The cheek was swollen and reddened.

This patient had extreme pain before entrance to this service. He had been keeping cocaine in his mouth on the areas, had required a good deal of morphine and had taken large amounts of whiskey to try to get relief. Operation in this instance was decided upon for the added reason of getting rid of pain.

A cautery excision of the growth with removal of most of the right mandible and part of the maxilla, and an upper right neck dissection was done. Two weeks later, radium was applied to the wound edges and neck. At the time of discharge from the hospital, pulmonary metastases were noted. The patient died two months later. The metastases were probably present, though unrecognized, at the time of operation. In spite of the wide destruction and the outcome, the patient and his family welcomed the relief from pain the operation gave. (Figure 11 A.)

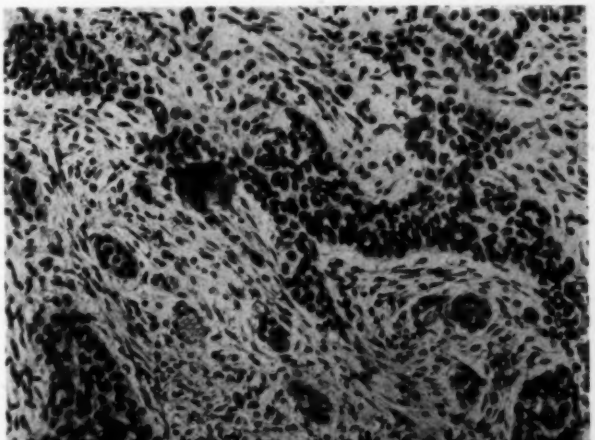

FIG. 16.—From the structure of the above section, it is difficult to say that this is a squamous cancer. Cell outline is indistinct and the nuclei are hyperchromatic. There is considerable variation in the size and shape of the nuclei. Mitoses are abundant. Many small lymph channels may be seen studded with the cancer cells. This tumor has been given a Grade 4.

Pathology.—Figure 11 B. Tissue removed from around the ulcer edge showed no carcinoma, but merely dense fibrous tissue. The section shown here was taken from a hard sclerotic area around the mandible. The stroma is dense and abundant presumably the result of radiation. The cancer cells show a moderate degree of differentiation. In other areas not shown here there is considerable hya'inization. The regional lymph glands in this case showed no evidence of carcinomatous invasion. It is interesting to note that cancer cells were found beneath the mylohyoid muscle. Whether or not radiation has influenced the differentiation of the cancer cells is a conjecture, as we do not know the picture of the primary growth.

CASE XII.—Male, fifty-six, white. Three weeks before the patient was admitted to the hospital, he noticed a small lump in the cheek.

Examination showed on the inner side of the right cheek a granular ulcerated tumor about 2½ centimetres in diameter, poorly defined and very hard. A few hard glands were felt just above the right clavicle.

A wide excision of this mass, including removal of the full-thickness of the cheek, was done with the actual cautery and several months later a neck dissection on the right side was performed. Following this he had a repair of the cheek. He is now well, twelve years after the first operation.

Pathology.—Figure 12 A and B. This is apparently a true adeno-carcinoma, papillary in type, and is the only one in this series arising in the buccal mucosa. Figure B is a higher magnification of an area shown in A. One sees villi containing a delicate fibrous tissue stroma and lined by well differentiated, low columnar epithelium. There were no demonstrable metastases to the regional lymph-nodes.

SUMMARY

(1) Cases are grouped into fairly definite anatomical sites chiefly because of their relation to treatment and prognosis, and to facilitate classification, history taking and presentation.

(2) The term "carcinoma of the jaw" is not used because bone involvement is secondary and only incidentally influences treatment.

(3) Growths with wide extension or metastases are put in the group corresponding to the primary growth site. Neck tumors do occur in which no primary growth site can be determined, but the majority of them are metastatic from some unrecognized upper respiratory or digestive tract growth.

(4) Four arbitrary clinical stages are distinguished and are of practical use in giving a basis for treatment and prognosis from clinical findings.

(5) Biopsies are done in most cases before treatment is begun, both for confirmation of diagnosis and for studying the relative degree of malignancy of the growth.

(6) In arriving at a plan of treatment and prognosis, clinical and microscopical findings are considered together. No one criterion has been found to offer a basis of prognosis accurate enough to present a percentage plan to the patient of his chances of life.

(7) Growths may for a time be held in relative abeyance, but later take on much more rapid growth if not a real increase in malignancy. In this series there is a higher percentage of undifferentiated growths in the late than in the early stages.

(8) There has been observed a type of growth that in clinical aspects is cancer, but in which the microscopic picture does not show the typical definition of cancer. These growths may cause great destruction if not treated at least locally as cancer.

(9) The degree of malignancy of metastatic gland carcinoma followed fairly closely that of the primary growth. There may be no microscopic evidence of malignancy in the regional glands, but this does not necessarily mean that the glands are not affected.

(10) Though results are, of course, best in the cases where no carcinoma was found in the glands, there are cases in the series that show that undifferentiated carcinoma even in the glands of the neck is not an absolutely hopeless situation.

(11) There is a high operative mortality, 21.5 per cent.; all but one of the deaths occurring in advanced cases where very radical operations had been done.

(12) The farther back in the mouth and pharynx the operation is carried, the higher the mortality. This is probably due to increased liability to respiratory infection.

(13) Results of treatment are tabulated.

DISCUSSION: DR. ROBERT B. GREENOUGH, Boston, Mass., said that there was no question in his mind that the work Doctor Blair has been doing in the plastic repair of very extensive excisions in cancer of the mouth has opened up a field of useful surgical treatment in a group of patients that have been left very much without help in the past. He was thoroughly in accord with the statement that if we can only rid a man of a sloughing, offensive local lesion within the mouth for as much as a year's time, even if after that he dies of more remote metastasis, we have accomplished a great deal for that particular man's good.

These extensive operations can only be done by making use of the principles of plastic surgery.

As to the grading of the degree of malignancy of the tumors in the decision as to just what is to be done in the individual case, he had been very confident that as time went on this principle would be more widely accepted. There is no doubt that what can be done in a tumor case of low grade malignancy may be bad judgment in one of higher grade.

The two following tables show the results of operation in a series of cases of cancer of the lip and cancer of the buccal mucosa which were graded into three and four groups of malignancy according to the amount of differentiation of the cells. The tables explain themselves.

TABLE I.

Cancer of the Lip; Results of Operation; Pathological Grouping.

	Living Cases	Per Cent.	Dead Cases
Group 1	53	81.5	12
Group 2	14	70	6
Group 3	4	22	14

Simmons and Daland (Surg., Gynec. and Obst., 1922, vol. xxxv, p. 766).

TABLE II.

Results of Operation; Pathological Grouping.

	Cases	Cures	Per Cent.
Group 1	17	12	68
Group 2	14	3	21
Group 3	17	1	6
Group 4	11	0	0

Simmons (Surg., Gynec. and Obst., 1926, pp. 377–382).

These cases were observed at the Massachusetts General Hospital and the Collis P. Huntington Memorial Hospital. The living cases were alive without evidence of disease three or more years after operation.

Doctor Blair had sent on to Boston a few sample slides from this series of cases that he has reported. Three different observers, Dr. Channing C. Simmons, Dr. H. F. Hartwell, surgical pathologist at the Massachusetts General Hospital, and the speaker had reviewed these independently. As a result of the examination of these fourteen specimens of different grades of malignancy, following the Broders classification of four grades, in only

two instances did the estimates fall more than one grade apart. In other words, they were practically all agreed upon the cases of high malignancy, and of low malignancy; and only in the middle groups were there differences of opinion as between Class 2 and Class 3, and these differences were virtually insignificant.

This would seem to demonstrate that in general the method of applying this gradation principle to cancer cases was being done in a reasonably uniform manner. There will always be some differences of opinion, since the personal equation enters so largely in the estimate.

In one respect their principles in Boston had been a little different from those suggested originally by Doctor Broders. In classifying the squamous-cell tumors of the skin and mouth he attempted to estimate the percentage value of differentiation in the whole tumor. Supposing there was three-quarters of the tumor that was well differentiated, and one-quarter of the mass that was less differentiated, Doctor Broders would grade the tumor at a lower degree of malignancy than in one where those percentages were reversed.

With us, we have taken the position that the most malignant bit of tumor tissue that could be observed in the whole tumor was the one which was to be considered, so far as the prognosis was concerned, and therefore, in a tumor which was generally of a low malignancy if areas were found that were distinctly of a high grade, the case is classed as one of high malignancy.

Dr. Channing C. Simmons, Boston, Mass., remarked that it is much easier to grade squamous-cell carcinoma pathologically than the œdematous forms, such as cancer of the rectum or of the breast, although this has been easier to grade squamous-cell carcinoma pathologically than the œdematous cancer. The clinical application of this is not yet entirely clear. It certainly is of great value in the prognosis of cancer of the buccal mucosa and lip, and has a distinct relation to the form of treatment which should be employed. For example, an extremely radical operation in this form of cancer is unnecessary if the tumor is of low-grade malignancy and small, while it should be done in every instance if the tumor proves to be of high-grade malignancy.

The term "cancer" applied to all the metastasizing epithelial tumors is in some ways unfortunate—cancer should be considered as a regional disease. There is nothing in common between cancer of the skin on one hand and cancer of the tongue and cervix on the other. A tumor that would be of low-grade malignancy in cancer of the tongue, Grade 1, is comparable to Grade 3 malignancy of the lip.

JUVENILE GANGRENE

By Walton Martin, M.D.
and
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from the first surgical division of st. luke's hospital

I have ventured to report four cases of gangrene of the extremities in young subjects, as such cases are unusual and their origin and manner of development imperfectly understood. I have thought it might be of interest to bring to your attention the reports of similar cases and to follow, as far as possible, the succession of happenings.

The first case, a boy four and a half years old, became acutely ill with temperature and symptoms suggesting a generalized infection. When seen three weeks after the onset, he had gangrene of the left foot, of both ears and of a circular patch of skin over the left patella. There was a systolic murmur over the apex of the heart and a to-and-fro pericardial friction rub heard over the sternum. The gangrenous areas separated and the foot sloughed through at the ankle-joint at the end of two months. The boy recovered and is well today, five years after his original illness. The skin over the stump of his leg, only a few inches above the original line of demarcation, is normal looking and movable. The skin of the stump of the ear is white and the scar looks as if a portion of the ear had been severed by a surgical operation. (Fig. 1, 2, 3, 4.)

The second case I have recently seen in consultation, through the courtesy of Dr. J. V. Bohrer of New York. A child six years old was lying in bed in a small flat. One hand and both legs were coal black, there were zones of suppuration where the living tissue was being separated from the dead. There was a recent healing scar on the external ear where a portion of dead tissue had fallen off. The boy had had an acute illness, apparently diphtheria, preceding the onset of gangrene. (Fig. 5.)

The third case, a boy seven years old, had widespread chronic tuberculosis. He had been chronically ill for six months with enlargement of the abdomen and cough when the left foot and lower part of the left leg became blue, swollen and tender. Gradually this gangrenous area became deep black and was separated from the living tissue. (Fig. 6.) Four months after the onset, when the soft parts had sloughed through to bone, an amputation was carried out through the thigh. The parts bled freely. The stump healed. Six months later the boy was still alive, although the general tuberculosis was more advanced. A section taken through the main vessels in the amputated leg showed endarteritis, confined largely to the intima. One of the veins showed some evidence of canalization as if it had been thrombosed. (Fig. 9.)

The fourth case, a boy of fourteen, had an indolent perforating ulcer on the ball of the great toe. In the course of three years he developed gangrene of the tip of the second toe and a perforating ulcer of the sole of the foot. The anterior portion of the foot was amputated. The stump healed soundly. The boy is well today and free from pain.

We have, then, four cases of gangrene in young subjects. The first and the second followed an acute general infection, in both of these the patches of dead tissue were multiple. The third occurred in a patient suffering from general tuberculosis with evidence of local endarteritis in the tissues above the

gangrenous leg; in the fourth local endarteritis was demonstrated in the foot, four or five inches from the gangrenous toe. The detailed report of three of these cases is given at the end of this paper, with the microscopical studies made by Doctor Shore of my staff, who has assisted me in its preparation.

In 1904, Barraud[1] published a paper giving the records of 103 cases of gangrene of the extremities, occurring in patients under thirty and following acute infection. The occasion of this essay was an unusual instance of gangrene of both legs in a woman of twenty, following an infection of the finger. The autopsy showed an arterial thrombus from the aorta downward.

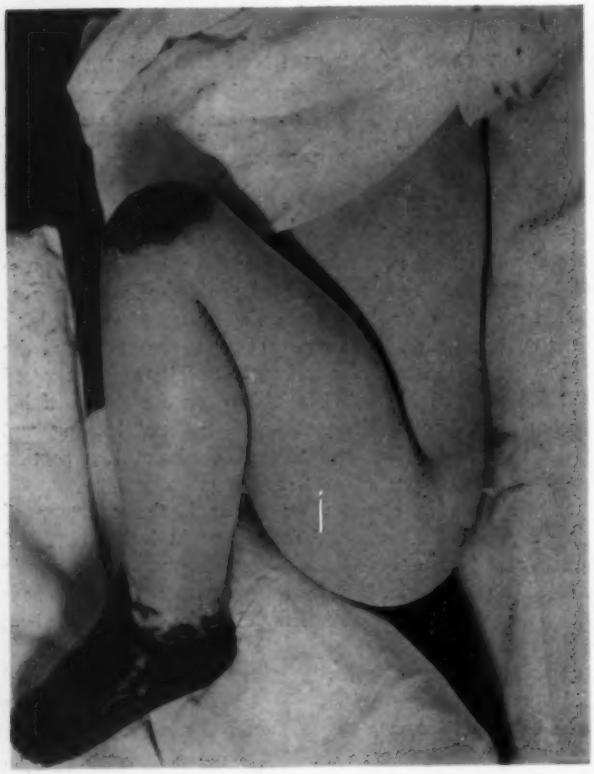

FIG. 1.
Case I. Gangrene of foot, and area over patella.

Among the cases he had collected, in forty-four the gangrene occurred in the course of typhoid and in eleven it followed typhus. In six the gangrene developed during measles; in five during scarlet fever; in two it followed diphtheria and in five pneumonia. In one case gangrene occurred after perityphlitis (appendicitis) in a six-year-old boy; in another, an eight-day-old infant, gangrene of both legs followed phlebitis of the umbilical vein. In still another, gangrene of the left leg, in a boy seventeen months old, was preceded by tonsillitis. Many of these cases are accompanied by autopsy reports or reports of examination of the large vessels after operation.

In 1914, Khautz[2] published a paper on "Spontaneous Gangrene of the Extremities in Children" and reported two cases, one in a child three years old, with gangrene of both feet and the lobes of both ears and a patch on the back of the hand. The gangrene was not preceded by any illness. Both legs were amputated; the patient recovered. No anatomical cause for the gangrene was found. The vessels appeared normal to the surgeon doing the amputation. No microscopical examination was made.

The second patient, a four-year-old boy, had gangrene of both feet. The

gangrene was preceded by an illness, possibly measles. Both feet sloughed off. The child recovered.

Khautz collected and published the records of fifty cases; thirty of these are the same as those reported by Barraud.

Every year or two, during the last twenty-four, similar cases have been reported. They are sufficiently uncommon to excite exceptional interest and are usually reported with the prefatory remark that the rarity of the condition has occasioned the publication and, for the most part, with reproductions of photographs showing the lesions. Between 1914 and 1925, Gerlach,[3] Veau and Weber,[4] Hoyne,[5] Hellstrom,[6] Gunson,[7] Robbins,[8] Chodax,[9] Michael,[10] Frenkel,[11] Thorpe,[12] Kramer,[13] Brusa,[14] Gordon and Newman,[15] Harrell,[16] Hoopman,[17] Perrier,[18] and Learmonth,[19] have all reported cases of gangrene in children, following infection.

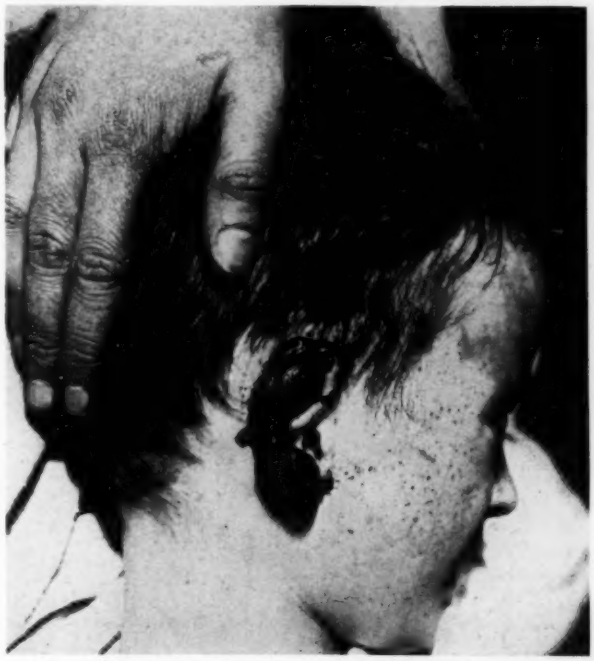

FIG. 2.
Case I. Gangrene of ear.

In looking back on the autopsy findings and the observations made on vessels of the amputated limbs in these reports, four groups can be distinguished. (1) The gangrene has followed an embolus, the primary thrombus being in the heart or the aorta; (2) there has been a primary thrombus in one of the large vessels supplying the extremity: (3) there has been evidence of local arteritis in the vessels above the gangrenous area; (4) no change has been found in the vessels up to the line of demarcation, there has been, presumably, a capillary thrombosis which has passed on to massive tissue death.

The gangrene has been preceded by acute general infection in so many instances in all groups that it seems probable that microörganisms or toxic substances liberated when microörganisms are growing in the body, are factors that cannot be set aside. It is also obvious that some unusual circumstance or combination of circumstances has been added, for it is a matter of common knowledge that measles, scarlet fever, diphtheria, typhoid and typhus fever, all manner of acute general infections, run their course commonly without any such phenomena.

The study, then, leads to a brief consideration of the occurrence of thrombosis under the influence of infection in the heart, in the large vessels, or in the capillaries of a given area.

As Aschoff expresses it, using a mathematical figure of speech, thrombosis is the function of a number of variables. There are factors that have to do with injuries to the endothelial lining of the various parts of the vascular system; there are factors that have to do with slowing of the blood current and there are those which have to do with alterations in the makeup of the blood. All these factors play a part but we are still ignorant of the order of their occurrence. Damage to endothelial cells by toxins, slowing of the current, deposition of fibrin, perhaps a few microörganisms caught in the fibrin meshes, further local destruction and the formation of a thrombus, may in some instances be the sequence. The dominant factor may be, on the other hand, a slowing of the blood current. The velocity of the flow may be reduced to a point where certain of the solid ingredients, like the blood platelets, settle out. It is even possible that the endothelium dies as the result of being covered over by platelets, as suggested by Aschoff,[20] and the institution of the changes leading to the separation of fibrin and the formation of clot may not be due in the first instance to damaged endothelium.

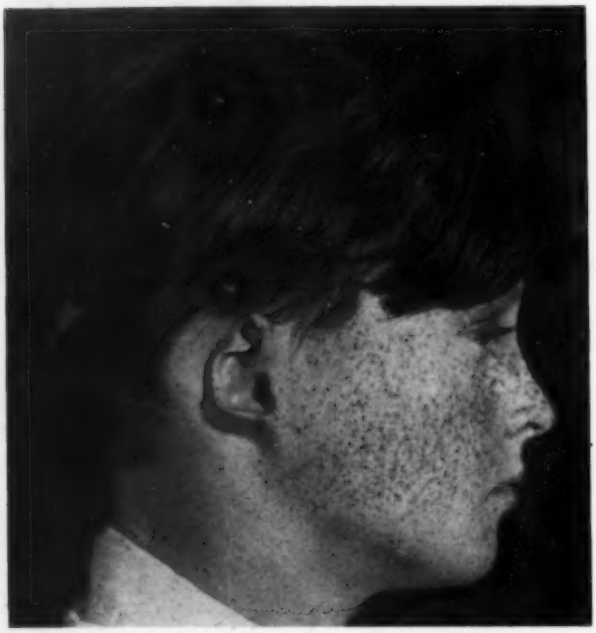

FIG. 3.
Case I. Five years later, showing deformity of ear following separation of gangrenous tissue.

It must be remembered also that there are altered relations in the blood itself, brought about by infection, which may act as a promoting factor. The circulating blood has floating in it a number of formed particles with different specific gravity. There are changes, in infection, in the numbers of leucocytes and probably also in the numbers of blood platelets, and possibly in the agglutinating properties of the platelets. There is a suspension stability for the various ingredients of the blood. Fahraeus[21] has shown that there is, at times, an increase of the globulins (fibrinogen) in the plasma during the reaction of the body to microörganisms.

Whatever the sequence of the factors may be, occasionally during the course of infection in children, not only are thrombi formed on the mitral

and aortic valves, but also in the heart cavities, especially in the auricle, and in the large arteries and in the small arteries and capillaries.

(1) When portions of a thrombus in the left heart or large vessels break off they are carried into the systemic circulation, forming emboli. Wherever an embolus lodges it becomes adherent and a secondary thrombus forms which extends peripherally, and to some extent centrally, producing thus not only blocking of the main vessel but shutting off, to a large extent, collateral circulation. Consequently, the probability of gangrene is far greater after an embolus than after ligation of a vessel, for the clot is then confined to the region of the ligature. These facts have been established not only at autopsy but by observations made by surgeons who have incised the large vessels and removed emboli and secondary thrombi from their interior. A paper by Einar Key,[22] published in 1922, gives interesting details of forty-eight cases in which embolectomy had been performed. All such emboli, though they have a definite relation to infection, do not set up where they lodge the forms of purulent inflammation which we are accustomed to associate with septic emboli. Local tissue death, due to cutting off of the blood supply, is the clinical result. Many autopsies, in cases of gangrene of an extremity in children and even in symmetrical gangrene of the extremities, have demonstrated the primary thrombus in the heart and the embolus or emboli in the extremity vessels. An instance is reported by Bull,[23] who pub-

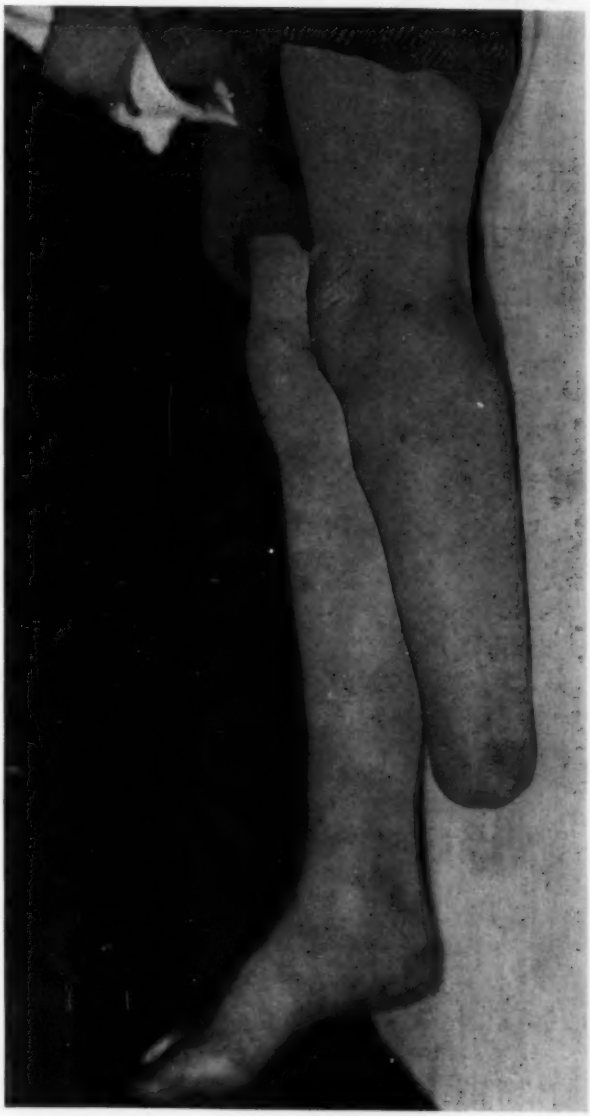

FIG. 4.
Case I. Five years after separation of gangrenous foot.

lished in 1922 a study of 6140 postmortem examinations with special reference to gangrene of the extremities.

A boy twelve years old had gangrene in the left calf and the toes of the right foot. He had had, before the onset of actual gangrene, attacks of pain in both legs, numbness and cyanotic coloring. He died suddenly. At autopsy the abdominal aorta was completely thrombosed from about the level of the renal vein. The thrombosis could be traced downward through both common iliac arteries. The collateral circulation was not examined. On one aortic valve there was a large "polypous grayish-white excrescence"; the other valve was normal. The relation to infection can also be seen in these autopsy reports; at least the autopsy records show both lesions of infection and thrombi in the heart. In a boy seven months old, with broncho-pneumonia and left sided empyema, the heart was large and at the apex of the right ventricle there was a firm thrombotic

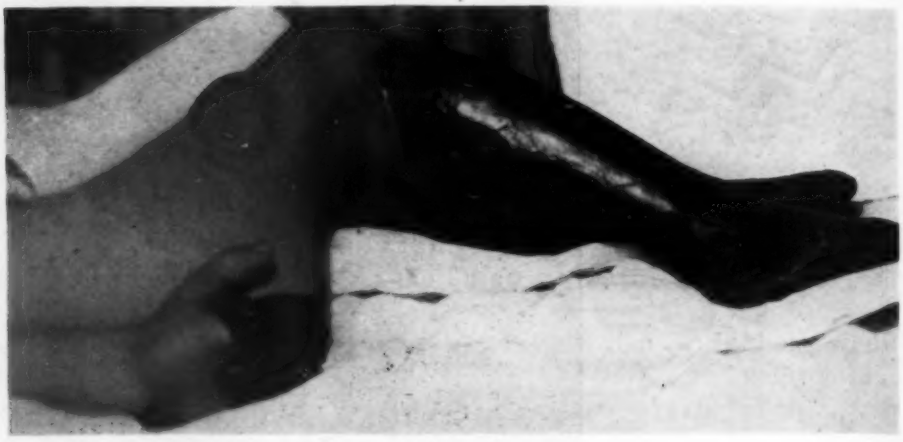

FIG. 5.
Case II. Showing gangrene of both legs and hand.

polypus, somewhat loosely fixed to the trabeculæ. In other instances the autopsy records showed a thrombus in the heart without valvular disease, hypertrophy, myocarditis or acute endocarditis. In a boy four years old, with general tuberculous infection, the heart is recorded as pale and flaccid. There was a thrombus three centimetres long in the left ventricle. In another, a boy twelve years old, with purulent arthritis of the knee, the heart was large, flaccid and pale; there were thrombi as large as peas in the right auricle. In still another, a boy eight years old, with acute osteomyelitis, the left ventricle was dilated, in the left auricle were brittle, crumbling thrombotic masses. In these cases, although no actual lesion of the heart was demonstrated, yet a thrombus formed which in most instances gave rise to emboli in the kidney, liver, brain, lungs and, once, in the arm.

In the case reported by Hellstrom (*l.c.*), the autopsy performed on a boy twelve years old showed at the apex of the left ventricular cavity a thrombotic mass adherent to the wall. In the aorta, four centimetres above the bifurcation, was a loose embolus two centimetres long which did not fill the lumen. In the right iliac there were a few small coagula. In the hypogastric artery (internal iliac) on both sides there were thrombi which completely blocked the lumen. The left femoral artery contained a few small clots, the right was filled with a partially organized thrombotic mass. He had been in the hospital suffering from a severe attack of diphtheria and had been given large doses of anti-diphtheritic serum. He showed signs of embolism and was operated on. At the time of operation the circulation had stopped in the right leg for at least thirty hours and in the left leg five hours. Both common iliac arteries were incised and thrombotic masses removed that extended as far as Poupart's ligament. The patient died the next day.

Evidence is also presented by the case reported by Harrell (*l.c.*), of symmetrical gangrene of the legs following pneumonia. The line of demarcation was present in the middle third of each leg. Both legs were amputated above the knee. The child recovered. The pathological report states that there was embolic blocking of both popliteal arteries. The embolus in the right popliteal artery was lodged at the origin of the anterior tibial, that of the left popliteal was a little higher up, behind the knee.

There can be no question that in certain instances juvenile gangrene results from embolic blocking of the vessels and that such occurrence has a direct or indirect relation to infection.

(2) A primary thrombus of a large vessel of the extremity has also been demonstrated a number of times.

Frenkel (*l.c.*) reported two cases of spontaneous gangrene of the extremities in children. One child was two years old and the other five. Both had tuberculosis. The autopsy report in the second case showed, besides the lung lesion, an adherent thrombus in the left popliteal artery, close to the bifurcation. The microscopic examination of the arterial wall showed inflammatory changes which correspond to the picture of a toxic arteritis. He refers to similar cases in adults such as the one reported by Schütt.[24] In no case was there evidence of the characteristic lesions of tuberculosis in the arterial wall, nor could tubercle bacilli be discovered in the arterial wall or the embolus. An interesting observation reported by Vaquez,[25] many years ago, though in an adult, is pertinent. A patient with advanced phthisis suddenly had an attack of pain in the left arm. The arm became cold and cyanotic. Pulsation ceased in the brachial and axillary artery. The patient died six days after the onset of pain. The autopsy showed lung tuberculosis with a large cavity. The heart was normal. The left subclavian was blocked by a thrombus adherent to the posterior wall; the lesion presented none of the characteristics of tuberculosis but streptococci were found in the walls of the vessel. The source of the streptococci was assumed to be the secondarily infected tuberculous cavity in the lung. The thrombus had formed in a tuberculous subject as a result of arteritis due to streptococci.

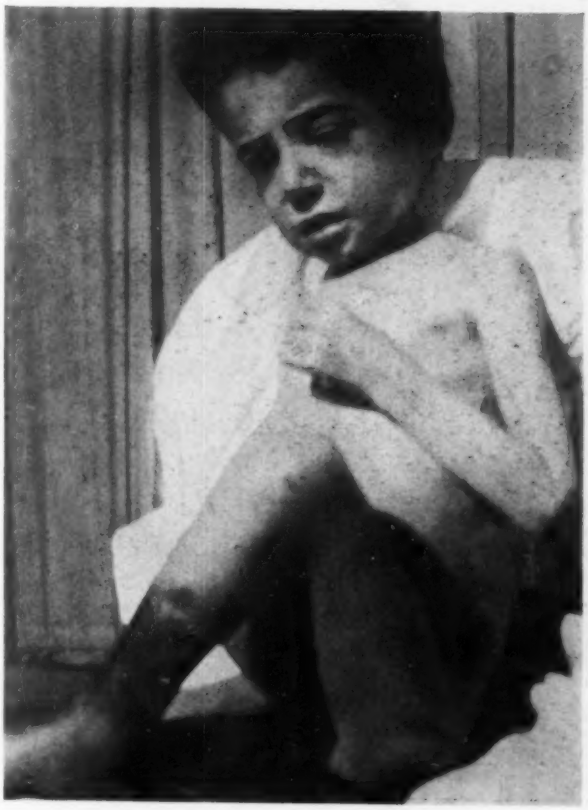

FIG. 6.
Case III. Showing gangrene of foot and lower third of leg.

It is well recognized that without an autopsy and even in some instances with an autopsy, it is difficult to distinguish between a local thrombosis and

an embolus with secondary thrombosis. The entire primary thrombus may be swept away by the rapidly flowing current and no trace of its origin can be discovered. Well recognized pulmonary emboli have been repeatedly demonstrated at autopsy and yet no thrombus discovered as a source of the embolism. In several of the cases reported, which have been observed carefully, no conclusion can be positively drawn as to whether an autochthonous thrombus or an embolus with secondary thrombosis is the cause of the gangrene.

FIG. 7. (Marcus Experiment 17)
Symmetrical gangrene produced by infection and local injection of adrenalin.

A case in point is one reported by Chodax (*l.c.*), of chorea complicated by gangrene of the fingers. A girl, aged twelve, had had chorea for one week when she entered the hospital. It was a first attack. There was no history of rheumatism and no history of shock or overwork. Two years previously she had had diphtheria and a bad attack of tonsillitis during convalescence. It was a moderately severe attack of chorea. There was a soft blowing murmur at the apex. Ten days later the right hand began to grow white and the finger nails blue. It was fully a week before gangrene of the finger and ball of the thumb set in. There was no pulse at the wrist. The pain gradually became very severe; the systolic murmur became much louder. The brachial artery could be felt like a cord along the arm. It is interesting to note that although the brachial artery was blocked, gangrene of portions of two fingers was the sole evidence of tissue death.

The explanation of the formation of a primary thrombus in an artery depends on the same factors as those already mentioned. The thrombus is found adherent to a portion of the arterial wall in which there is local damage to the endothelium. The conspicuous clinical feature is again the death of tissue distal to the blocked vessel, not inflammatory phenomena set up at the site of the thrombus.

It is difficult to think of such local action on the endothelium being produced solely by circulating toxins, although diffuse changes have been repeatedly demonstrated experimentally.[25, 27]

In several instances microparasites have been demonstrated in the walls of vessels. From the phenomena presented they must be of low virulence or deposited in a refractory subject after an altered reaction has been established in long-standing infection. It is difficult to imagine sufficient slowing in the rapidly moving arterial current to let the platelets settle out sufficiently to initiate fibrin formation and coagulation or to enable contact with the endothelium long enough to have the cells take up microörganisms. An explanation often given is that the local endothelial damage which originates the thrombus is set up by changes in the nutrient vessels of the arterial wall. There is probably the same difference in velocity between the flow in the

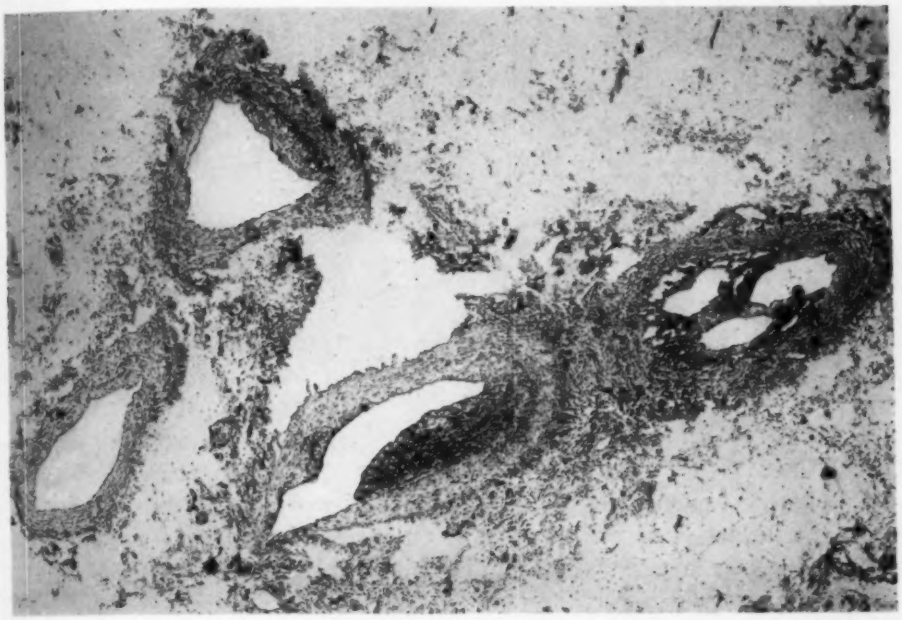

FIG. 8.—R. A. Photomicrograph of the popliteal artery and accompanying veins, showing the fibrous tissue proliferation of the intima with a reduction in size of the lumina. x 20. Case III.

capillaries, into which these nutrient arteries break up in the vessel wall, and the main arterial current that there is elsewhere. The rate of flow, as given in physiologies, is sixty to 120 times slower in the capillaries than in the large arteries.[28]

The anatomies give little information regarding the vasa vasorum. Porrier,[29] in the volume on the blood-vessels, has only a very brief statement. In 1922, Ostrogorski published in Russian a monograph on "The Nutritive Blood Supply of the Main Arteries of the Extremities". An abstract of his paper was given in German in 1923.[30] Ostrogorski examined seventy-six arterial stems. The femoral, the popliteal, the tibial, the brachial, the ulnar and the radial arteries were all studied by means of difficult and elaborate methods of injection and staining. (Gerota, Teichmann.) Most of the vasa vasorum spring from the small branches supplying the neighboring muscle.

The immediate branching of small nutrient vessels from the main vessel is rarely observed. The slender vessels follow, for a time, the arterial stem which they nourish, then pierce the adventitia and gradully lose their identity in the muscular walls. They nourish the adventitia and the tunica media. The intima, under normal circumstances, contains no vasa vasorum. The angle of entrance is usually obtuse, rarely retrograde. Some of the minute vessels break up shortly after they are given off into a number of fine branches. All run parallel to the arterial trunk and the parallel branches anastomose freely with one another. The number of separate branches is not the same for all arteries. There are zones of poor vascularity in the vessel walls.

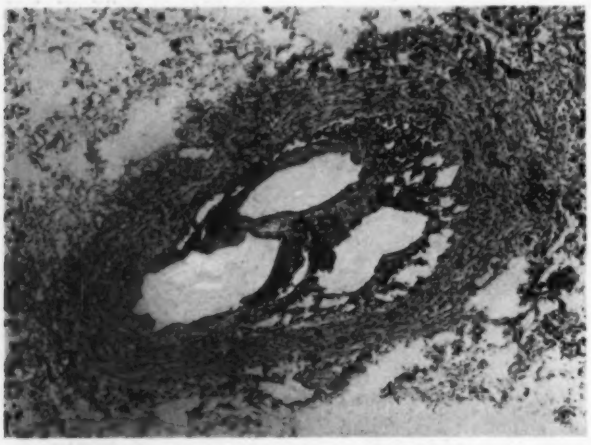

FIG. 9.—R. A. Photomicrograph of a higher magnification of one of the popliteal veins shown in Figure 8. The lumen is partially occluded by fibrous tissue which in places is canalized. x 60.

The succession of events is, possibly, alteration in the endothelium and thrombosis of the minute capillaries of the arterial wall where the circulation is slow and the time of contact of the toxic agent prolonged; then local arteritis resulting in gross damage to the endothelium of the vessel itself. Blood platelets become adherent to this damaged area, there is a separation of fibrin, the formation of a small white primary thrombus, then a mixed thrombus and finally, a large red thrombus blocking the lumen of the vessel.

(3) In a very considerable number of extremities removed at operation, careful examination has demonstrated neither an embolus nor a thrombus in a large vessel. There is a local endarteritis with narrowing of the lumina in the vessels above the area of gangrene. Two of the cases I have reported show such lesions. The change in both instances are strikingly similar. It must be remembered that in both the process had been present for months before the parts were amputated. In both the essential lesions found at the time of amputation were endarteritis and endophlebitis. The intima was thickened by an increase in connective tissue. In some places, especially in the minute arterioles, this new tissue was almost sufficient to occlude the lumina. The endothelium was intact; there were no thrombi in the vessels in the area examined. In one vein there was evidence which might be interpreted as originally thrombosis with subsequent organization and canalization. (v. Cases III and IV.)

There were somewhat similar findings in a case reported by Kramer (*l.c.*) in which there were irregularly-shaped and various-sized patches of discolora-

tion on the upper and lower extremities and gangrene of the left foot. The patient was a child about eight years old. He had been ill one week when the gangrene began. Amputation was performed above the knee twenty-four days later. Nine sections were taken from different areas in the amputated limb. They showed varied lesions in the vessels. The large arteries showed thickening of the media. At one point one large artery showed what appeared to be a very early and slightly marked necrosis. Opposite this was a thrombus firmly attached to the intima. The endothelial coats at this point had been lost. In all the sections the small arteries showed a thickening of the media resulting in a narrowing of the lumina to about one-third or more of their diameter. No thrombi were found in these vessels.

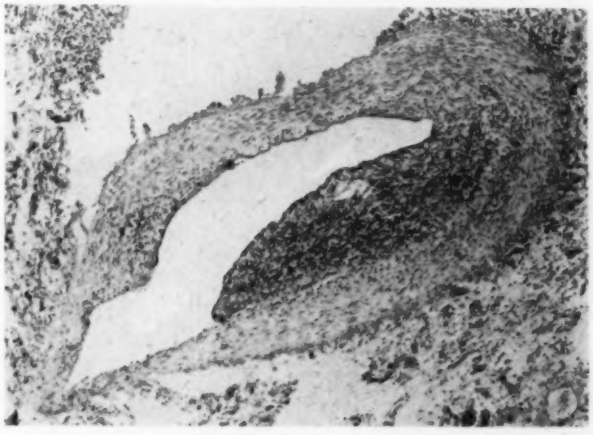

FIG. 10.—R. A. Photomicrograph of a higher magnification of the popliteal artery shown in Figure 8. There is a marked proliferation of the fibrous tissue of the intima with a great reduction in size of the lumen. x 60.

There can be little question of a group of cases of juvenile gangrene due to widespread changes in the walls of the smaller vessels. There is here, again, some connection with infection. Kramer assumed a relation with strains of streptococci, the portal of entry being the throat. The clinical signs that arrested attention were gangrene, trophic disturbance and purpura.

It seems from the last case I have reported that a localized endarteritis may occur in young subjects which is so subacute that the symptoms escape attention. There is no extensive thrombosis or gangrene until injury or infection occurs in the area which is poorly supplied by blood through narrowing of the lumina of the vessels. This form may represent an instance of mild infection of the small vessels of the same order as is seen in the severe instances with subsequent gangrene.

Experimental work has shown that when the intima is damaged by toxins or by microörganisms the damage is most marked in the capillaries and smaller vessels. That is to say, both toxins and microörganisms seem to produce most damage to the endothelium of the vessel walls when contact is most prolonged. The damage to the smaller arterioles is proportionally much greater than in the larger in the fourth case report. (v. Fig. 13.)

(4) Finally, there are cases of gangrene where no embolism of a vessel nor autochthonous thrombus nor arteritis has been demonstrated at autopsy or in an amputated limb. A striking instance is the case reported by Hoyne (*l.c.*) in 1915.

The child was five years old and died of broncho-pneumonia. He had, while in the hospital, scarlet fever, measles, double otitis media, swelling of the parotid, varicella and whooping cough. About 8 A.M., the forty-sixth day after the onset of scarlet fever, the thirtieth day after the onset of measles, the ninth day after the varicella and the seventh day after the beginning of whooping cough, large patches of a bluish-black hue appeared on the dorsum of the feet, near the base of the toes and smaller patches on the back of the right wrist and right cheek. By the evening of the same day the patches had enlarged and the lower half of the right leg was involved. The same day an area developed on the left cheek. All the areas were sharply defined and extremely painful. The skin above the cyanotic areas on all four extremities had a swollen, tense, waxy appearance. It looked œdematous but was rather hard, did not pit and was very painful. By the second day both ears were discolored over the upper half and became black and cold. The lower extremities began to look gangrenous but there was no extension of the process. Two fingers of the left hand and three on the right were also affected. On the third day examination of the chest showed a broncho-pneumonia and the temperature was 103° F. On the fourteenth day the child died as a direct result of pneumonia.

FIG. 11.—X-ray of bones of stump taken two years after amputation. Case IV.

The autopsy, performed by Prof. Gideon Wells, showed that the thymus was smaller than normal and that the thyroid was somewhat enlarged and succulent; the heart was normal in size; there were no changes seen in the aorta and the valves were normal. The lower lobes and the lower half of the upper lobes of the lungs were consolidated. The kidneys were very pale, somewhat firmer than normal. The adrenals were enlarged. The vessels of the lower extremities showed no evidence of thrombosis or embolism. The right femoral vein showed a large ante-mortem clot believed to be secondary to the gangrene and of recent formation.

Histologic examination gave no definite findings which could throw light on the etiology of the gangrene. Bacteriologic examination was made. Cultures taken from the

thrombus of the right femoral vein showed a green streptococcus and a hemolytic streptococcus. Injected into rabbits, these caused a malignant endocarditis.

In a number of instances in which the patients have recovered, the gangrenous area or extremity has sloughed off and there has been no specimen obtained by amputation through living tissue well above the gangrenous area which could be examined and studied. However, it is difficult in these cases to believe that embolism or an autochthonous thrombus in a large vessel is the source of the gangrene. For example, the blood is supplied to the circular

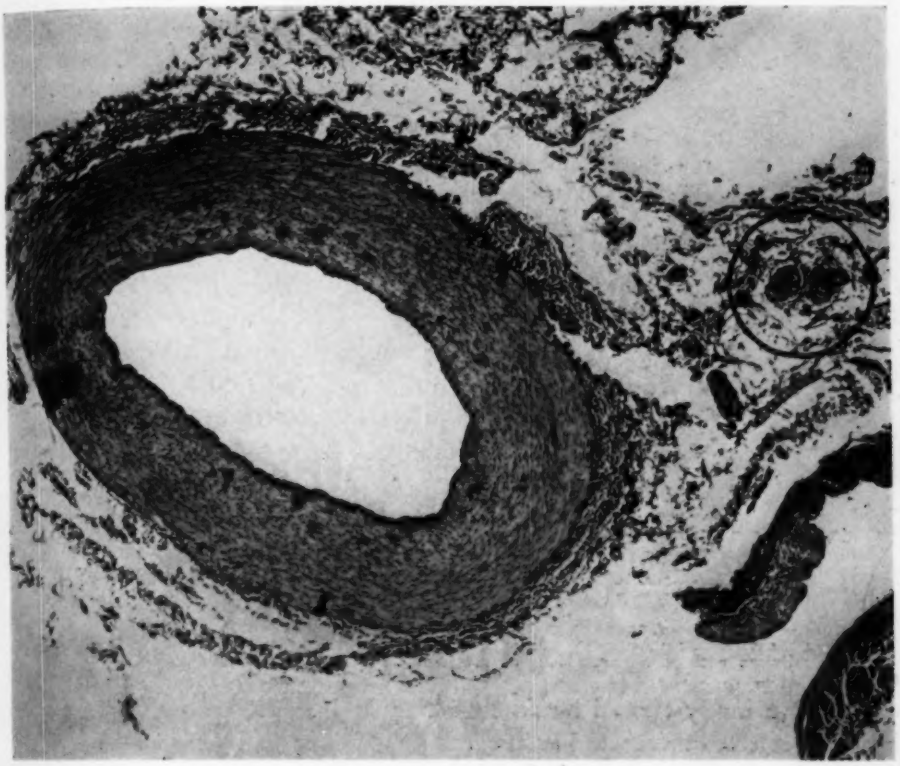

FIG. 12.—J. B. Photomicrograph of the plantar artery showing thickening of the intima. The partially occluded arteriole and venule in the circle are shown with greater magnification in Figure 13. x 30. Case IV.

skin area over the knee through a number of anastomosing small arteries. It is difficult to think of this area being shut off except by capillary thrombosis, yet there was gangrene in this area in the first case that I have reported. The same is true of the blood supply of the external ear.

In the case reported by Brusa (*l.c.*) of symmetrical gangrene of the hands in a child of fourteen months, it is again difficult to think of double embolic blocking of the brachial arteries producing the lesions, and the same may be said for the second case I have reported. In Brusa's case the gangrene was apparently not preceded by an acute infectious disease. In the beginning of November the child began to complain at night, was excited and rubbed the hands together as if they were irritated. It was noticed that they were œdematous and livid. There was a slight fever. The feet were involved in

the same way. The color of the skin was dark, especially over the great toe. The skin of the extremities showed marbling, clear areas alternating with purplish. Finally, along a line one and a half centimetres above the fold of the wrist, one saw a zone of demarcation appear. This line was several millimetres wide and festooned. The hands became œdematous, large blebs full of sero-sanguineous fluid formed. The great toe turned black.

Von Pirquet and Wassermann tests were negative. The spinal fluid was normal.

One month and twelve days after the onset the left hand became detached and fifteen days later the right. A portion of the great toe also sloughed away. The general condition improved gradually and all the granulation wounds healed normally. It is interesting to compare this case with Chodax's case (*l.c.*), in which only the tips of the fingers became gangrenous, yet the whole brachial artery was evidently blocked.

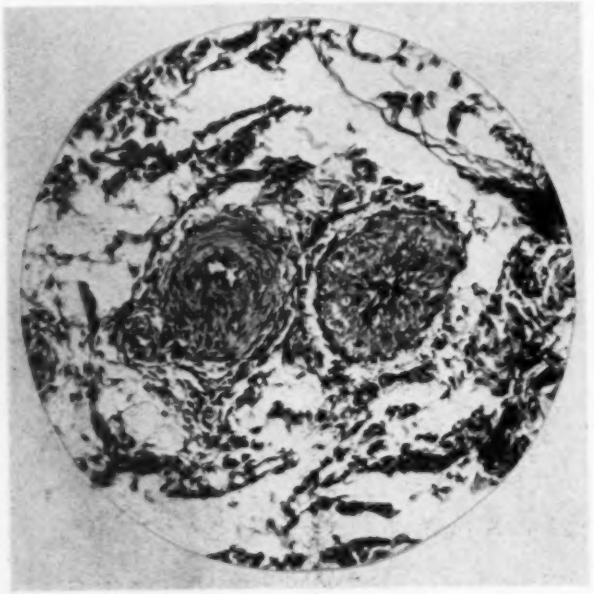

FIG. 13.—J. B. Photomicrograph of the arteriole and venule included in the circle in Figure 12. It shows the marked proliferation of the intima with partial occlusions of the lumina. x 140. Case IV.

In 1921, Marcus[31] made a series of interesting experiments in rabbits. He injected, twice a day for eight days, into the ear vein of rabbits, doses of adrenalin sufficient to blanch the ear for several hours. He then injected into the vein of the other ear, or into the leg vein, a dose of streptococci too small to kill the animal but sufficient to create a low grade general infection. There was no effect in the ear not previously treated by adrenalin. In the ear in which the adrenalin had been injected there was local gangrene. Microscopical examination of the changes in the damaged ear, before the parts had become gangrenous, showed widespread hyaline thrombosis, damage to the lining endothelial cells and round cell infiltration about the capillaries and minute vessels. He varied the experiments in a number of interesting ways. He was not able to produce gangrene either by adrenalin alone or streptococci alone. His paper shows reproductions of photographs of fourteen rabbits with various forms of gangrene of the ear.

I have reproduced Figure 4 (experiment 17) showing symmetrical gangrene. (Fig. 7.) Adrenalin was injected subcutaneously in the left ear of the rabbit twice daily for eight days. There was no fever and no gangrene. Marcus then injected streptococci in the right ear intravenously. A lesion appeared in the left ear (that is, in the ear previously treated with adrenalin). He then repeated the streptococcal injection several times to produce a more

long-standing infection. The right ear remained sound but injection into this ear of adrenalin caused a patch of gangrene. The introduction of adrenalin, which in itself produced no tissue death, so altered the resistance of the endothelium of the small vessels that subsequent injection of streptococci caused widespread capillary thrombosis and tissue death; and when a streptococcus infection was established the introduction of adrenalin produced enough change in time of contact or interference with nutrition to produce again hyaline thrombosis and gangrene.

We are all, I think, familiar with the curious local spasm of the vessels in the fingers called local syncope and local asphyxia. We have clinical evidence of a similar condition of spasm of the vessels of the hands and feet occurring in children.

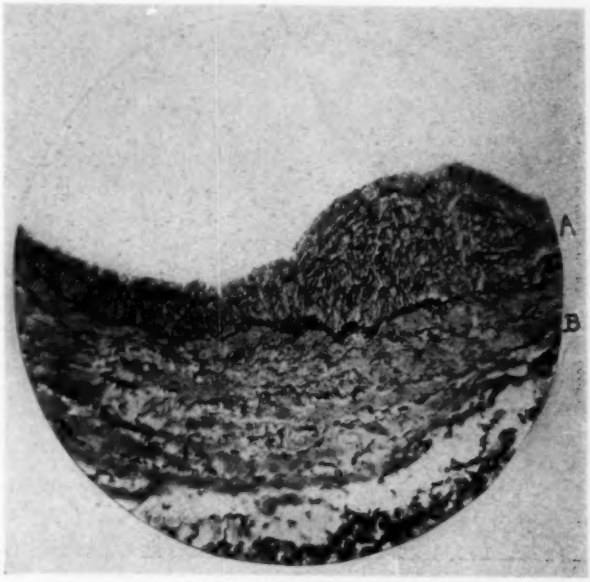

FIG. 14.—J. B. Photomicrograph of a portion of the wall of a vein stained for elastic tissue. It shows the marked proliferation of fibrous tissue inside a poorly defined internal elastic lamella. A.—Intima. B.—Media. x 50. Case IV.

The case reported by Lederer[32] in 1914, is significant. A boy, six years old, suddenly cried out with severe pain in the hands and feet. On undressing him the mother noticed that both hands and feet had become blue. The hands returned to normal in two hours but the change in color became more marked in the feet and the mother became alarmed and brought the child to the hospital. He had always been well, had had none of the infectious diseases; there was no history of syphilis or tuberculosis. Examination showed a well developed, strong child. There was a slight elevation of temperature. Both feet and the lower half of the legs were deeply cyanotic. The alteration in color was sharply defined. The legs and feet were very sensitive, cold and œdematous. After several hours the legs and feet became warm again and gradually resumed a normal appearance. Two days later the left hand suddenly became cyanotic and œdematous. The fingers were cold to the touch. Again there was a sharp line of demarcation. The pulse of the left radial artery seemed weaker than that of the right. This condition lasted five hours, then the parts returned to normal. The next day both feet were affected. The attack lasted three hours. Two days later both feet became cyanotic and cold and extremely painful. The child lay with the legs drawn up. The attack lasted two hours. The parts then returned to normal, the attacks ceased and no gangrene developed.

It must be remembered that Raynaud's thesis was written in 1862.[33] His admirable article, covering the whole subject of gangrene, appeared in the Nouveau Dictionaire de Medicine et Chirurgie Pratiques in 1872,[33] before there had been any widespread recognition of the startling induction made by

Pasteur that all infectious diseases were due to microörganisms. Have we not here a possible explanation of the third stage of Raynaud's disease? Infection is added to local spasm. This is the view expressed by Marcus. (*l.c.*)

An instance of curious spasm of the vessels of the extremities is reported by Holsclow and Booth.[34] An infant six weeks old was given by mistake seventeen minims of obstetrical pituitrin, administered in six doses between 10 P.M. and 12:30 A.M. The hands and feet became a deep purplish color and very cold. There was a sharp line of demarcation. The distribution of the lesions was curious; the right hand and half way up the forearm, the left hand, except the thumb; on the right foot the big toe and the second toe; almost the entire left foot. The child died the following day. A complete autopsy revealed nothing except that the arteries seemed small, as if contracted.

FIG. 15.—J. B. Photomicrograph of a portion of the wall of an artery stained for elastic tissue. The proliferation of fibrous tissue which is rich in elastic fibres inside the internal elastic lamella is shown. A.—Intima. B.—Media. x 50. Case IV.

The study of etiology brings up the question of treatment. Amputation, embolectomy and operations on the suprarenal have been suggested in the different forms.

For many of these small patients, high amputation has been advised. The surgeon has been influenced by the knowledge gained in treating gangrene in old people, in which it is generally recognized that it is desirable to amputate well above the gangrenous area, through the thigh for gangrene of the foot, for example. I believe this is unnecessary. If there is dry gangrene of the extremities, it seems to me a far better practice to let the dead soft parts separate and sever only the bones or tendons, refashioning subsequently if a poor stump results. My own observations and case history after case history, show stumps with good nutrition and vigorous healing almost down to the gangrenous area. The analogy drawn from senile gangrene is unsound. Protecting the area from injury, keeping the skin margin along the line of demarcation scrupulously clean, making every effort to avoid secondary infection of the granulating area and attention to the general health, are essential.

The question of removal of a portion of one of the suprarenals was brought into prominence by W. A. Oppel of Leningrad, in 1921.[35] Such

treatment could only have come in question in the fourth patient in my series. I give the abstract of the history of a similar case, but in an older patient, reported by Leriche [36]

A portion of the suprarenal was removed in a patient of thirty-two, who had trophic disturbances in the foot, pain, contracture and a necrotic ulcer. Leriche had already amputated a toe and performed a periarterial sympathectomy on the common iliac and femoral arteries a year before without relieving the symptoms. He reports the results as surprising. The pain disappeared instantly, the contracture and flexure disappeared; the ulcer cicatrized. Six months later he was still well and thoroughly satisfied with the success of the treatment.

The theory advanced by Oppel, that certain forms of spontaneous gangrene are a consequence of the hyperfunction of the suprarenal and that this throws into the organism, in inflammatory diseases, an unusually large amount of adrenalin which produces spasm of the blood-vessels of the extremities and thereby also of the vasa vasorum, resulting in interference with the nutrition of the vessel wall, is interesting. He has presented his views recently [37] and believes that the discussion has been settled theoretically and that a hyperadrenalemia actually exists in both spontaneous gangrene and in Raynaud's disease. These views have, by no manner of means, been universally accepted. It seems to me that the scientific evidence is as yet insufficient to furnish sound indications for the removal of a portion of the suprarenal in a case such as I have described. In all these discussions, as in the discussion of thrombosis, we are evidently dealing with multiple factors. The cause is not simple or single; it is complex and multiple. The increased output of the suprarenal may be a contributing cause. But the permanent control of this excessive output by the removal of a portion of one gland seems to me unlikely.

In regard to embolectomy, the brilliant work of Einar Key stands out. He reported in 1922 the results in eight cases in which he had performed the operation. These operations, however, were performed for threatened gangrene, not for established gangrene and the patients were adults. I have reported the results in a boy of twelve operated on by Hellström. The difficulty of early diagnosis, the fact that the children for the most part have been very seriously ill from general infections and that a general anæsthesia would be necessary, that the vessels are small and that incision into the walls may well set up a widespread thrombosis, makes the procedure seem ill-advised in children.

To Summarize.—Gangrene in children, even symmetrical gangrene, is not an entity.

Some of the cases are due to embolism; others are due to autochthonous thrombi; still others are due to endarteritis of the minute vessels and capillaries, and spasm of the vessel seems to play a part.

Nearly all the reported cases have occurred during the terminal stage or subsequent to a generalized infection.

Experiments on rabbits show that the minute vessels of the extremities

can be so altered by a combination of the local injection of adrenalin and the intravenous injection of small doses of streptococci that capillary thrombosis occurs, followed by gangrene.

Both sequences occur, producing tissue death: spasm, then infection and infection followed by spasm.

There is a clinical record showing that spasm of the vessels, with a curious local distribution, may occur after the administration of pituitrin in an infant.

The use of the term Raynaud's disease for all cases of symmetrical gangrene is misleading.

Case I.—(Figs. 1, 2, 3, 4.) R. N., a child four and a half years old, was referred to St. Luke's Hospital, March 29, 1923. He was a well developed boy, appearing as if he had suffered and was still suffering from a severe illness. The physical examination was negative except for a systolic murmur heard over the apex of the heart and a to-and-fro pericardial friction rub heard over the aortic region and along the sternum and to the right of the sternum in the fourth interspace. The pulse was rapid and feeble. The temperature was 101° F. The left foot was coal black and cold. There was a sharp line of demarcation just above the ankle-joint. Above this there was a circular zone slightly reddened and suppurating where the beginning ulceration was separating the living from the dead tissue. The leg above was œdematous; over the patella was a similar circular gangrenous area about five centimetres in diameter. The right leg and foot were œdematous. There were several small areas on the right foot appearing as if they had recently healed after being denuded of epithelium. There was a bleb on the tip of the right middle finger. Two-thirds of the right external ear was cold and black, with a sharp line of demarcation separating the living and dead tissue. The outer margin of the left external ear showed a similar condition. Lips, teeth and mucous membrane of the mouth and tongue and pharynx were normal. The tonsils were moderately enlarged. There were no enlarged lymph-nodes.

The mother stated that the child had been taken suddenly ill three weeks before with difficulty in breathing and cough and a high temperature. He complained of pain all over and particularly when touched. He seemed to have difficulty in swallowing, vomited and complained of abdominal pain. The pain became more and more severe. The child had slept little and cried out from time to time.

After three days his general condition improved; he sat up in bed. At the end of a week his legs became extremely painful. An area over the left ankle and heel became bluish and a bleb formed. At the same time a similar area formed over the patella. Within a few hours the right ear became greatly swollen and turned purple. The following day similar changes took place in the left ear, but they were less marked. The penis became swollen and several blebs appeared on the prepuce.

The areas affected were all exquisitely painful and acutely sensitive to external impressions and all the lesions except that on the penis had passed to the condition of gangrene seen at present.

The child was one of twins and had always been well except for an attack of influenza with bronchitis two years previously. The family lived in a cold, damp house and the mother thought that the child on several occasions became seriously chilled. There was no history of freezing or frost bite of the ears or feet.

The mother was so excited by the nature of the illness and the feeling that portions of the child were dying under her eyes, that it was difficult to obtain a consecutive story of the illness, but the facts seem to have been as related. Wassermann reaction was negative.

The patient was referred to the medical service as the indications of pericarditis and endocarditis and the acute illness seemed to be the urgent features and the advice

was given to protect the gangrenous areas from trauma and to keep the sulcus forming along the line of demarcation as clean as possible.

One by one the gangrenous areas separated. The foot sloughed through at the ankle-joint at the end of two months. Without any anæsthetic the ligamentous attachments which held the foot to the leg were severed. Except for this there was no surgical interference. After the dead tissue was detached the parts rapidly healed.

The specimen of the foot removed was hard, dry and black. The articular cartilage was partially absorbed. There was no sound tissue from which to take a section for microscopical study.

The skin sloughed through at a level with or even higher on the leg than the joint, so that a conical stump was expected and the mother was advised to bring the child back for removal of the bone ends and the fashioning of a sound stump.

Two and a half years later a small portion of the fibula was removed and the conical stump was revised. During this interval the boy had had measles, whooping cough and chicken pox. He was examined in March of this year, five years after the operation, and was a well grown and sturdy boy. The skin over the stump was movable and the nutrition excellent. The stump of the right ear showed no abnormality. The skin was white and the scar looked as if a portion of the ear had been severed by a surgical operation. The heart sounds were normal; there was no thrill or sign of hypertrophy.

Case III.—(Fig. 6.) R. A., a Syrian boy seven years old, was admitted to the Pediatric Division of St. Luke's Hospital in July, 1913. The child had been normal until six months before admission when a moderate, gradual enlargement of the abdomen was noticed and he began to cough. He had been in St. Mary's Hospital, suffering from these symptoms, for two months. Four days before admission the left foot and lower part of the left leg became blue, swollen and tender.

Physical examination showed a poorly developed and nourished boy, slightly cyanotic; the cervical, axillary and inguinal glands were slightly enlarged. Pulses were equal and regular. The tongue was covered with patches (called "stomatitis") but did not seem tender. Below the angle of the right scapula there was dulness and bronchial breathing, extending into the lower axilla. The heart showed no lesion. The abdomen was enlarged and the liver percussed to the sixth rib, the lower border being at the level of the umbilicus. The surface of the liver was firm and not nodular; the spleen was not felt. There was shifting dulness in the flanks.

The left foot and lower half of the left leg were blue, slightly swollen, tender and cold. The toes could not be moved. There was loss of sensation to touch and temperature. The foot was not sensitive to pain. The upper edge of the discolored area was sharply marked, although the color was lighter along this line. The knees were held in flexion and seemed painful on motion. The knee jerk was not obtained on this side. The right knee jerk was present. There was no Babinski, clonus or Kernig.

The urine was negative except for a very faint trace of albumin. Examination of the blood showed hæmoglobin 90 per cent., red blood cells 4,800,000, white blood cells 14,000, polymorphonuclears 78, lymphocytes 22. The morphology of the blood was normal. The blood culture on two occasions was negative. Nose and throat cultures were negative for diphtheria. For several months the daily temperature varied from 98° F. to 102° F. The pulse varied from 120 to 140. The respirations averaged between 38 and 65. Soon after admission the patient's right chest was tapped and thin, straw-colored fluid was removed. This was repeated several times while he was in the hospital. The abdomen was also aspirated five times and clear, straw-colored fluid, with a specific gravity of 1020, removed. A guinea pig injected with this fluid was negative for tuberculosis. Analysis of the Syrian bread and flour for ergot was negative. Intradermal luetin test was negative. The foot gradually became darker and a more definite line of demarcation was present.

Four and a half months after admission the left leg was amputated about six centimetres above the knee joint by Dr. W. A. Downes. The wound healed without difficulty.

The macroscopical examination of the specimen showed a leg amputated above the condyle of the femur. The foot and lower third of the leg were completely dried, blackened and mummified. At the line of demarcation there was a separation of tissues as deep as the bone, except for two tendons posteriorly. An intermission was left between the healthy and the mummified skin three centimetres posteriorly, two centimetres mesially and two centimetres laterally. The line of separation began internally six centimetres above the malleolus and ran diagonally upward to eleven and five-tenths centimetres above the external malleolus. Normal skin had grown inward and practically covered the upper edge of the muscle. The end of the skin ran down almost as far as the bone.

Microscopical Examination.—The one section of the vessels and nerves taken for microscopical study is presumably from the popliteal region as the remainder of the leg is mummified and was not dissected.

Artery.—The lumen of the artery is reduced to about one-fourth of its original size by a marked proliferation of the sub-endothelial connective tissue. There is a vacuolization of many of the new cells and a round cell infiltration throughout. This new tissue contains several capillaries in which are seen partially degenerated red blood cells. The endothelium is everywhere intact and smooth. The internal elastic lamella is intact. The muscle fibres of the media show mild degenerative changes and a moderate round cell infiltration. (Fig. 10.)

Veins.—The three veins accompanying the artery show essentially the same lesions, varying only in degree. There is a sub-endothelial proliferation of connective tissue which in places shows degenerative changes. In one of the veins this proliferating tissue had bridged the lumen in several places, so as to divide it into multiple channels. These fibrous areas contain capillaries and many large mononuclear cells with hemosiderin pigment. The endothelial lining is intact. The adventitia and media show only a round cell infiltration. (Figs. 8 and 9.)

Nerves.—Cross-sections of the nerves show degeneration of the axis cylinders and a moderate amount of round cell infiltration.

Discussion.—The vascular changes in this and the following case are essentially identical. An endarteritis and endophlebitis are the prominent lesions. The only added pathological change which is open for speculation in the present patient, is as to the exact process which preceded the canalization of one of the veins. An original thrombosis, with subsequent organization and canalization, is to be considered but the presence of sub-endothelial thickening in the other veins, identical except for the bridging of the lumen, is more in favor of an obliterating endophlebitis, without thrombosis. The proliferation of the sub-endothelial connective tissue and the diffuse round cell infiltration are the reactions expected following injury to tissues. The injury in this case may be infectious or toxic. There are no lesions in the amputated part which in any way resemble tubercles.

The boy was discharged improved from the hospital several weeks later, but returned in two and a half months, the abdomen being again swollen. The amputation stump was well healed; the right leg was thin, small, but showed no œdema. The abdomen was tapped several times and the patient was discharged after three months, slightly improved. One month later he was admitted to Bellevue Hospital. The records there showed that an exploratory laparotomy was performed. The peritoneum, intestines and liver were everywhere studded with firm, yellowish nodules, varying in size from the head of a pin to a hazel nut. The pathological report from sections removed at operation showed tuberculosis. The abdominal wound healed and the child was discharged from the hospital. He returned one month later, showing a large swelling on the outer side of the left elbow. It had been opened several days before in the Out Patient Department and was discharging pus. The incision was enlarged under general anæsthesia. Seven days later he was again discharged from the hospital with a diagnosis of tuberculous abscess of the left elbow. The records at Bellevue show no later admission, nor a notice of death.

Case IV.—J. B., a boy fourteen years old, entered St. Luke's Hospital in Novem-

ber, 1924. He had a discharging sinus on the ball of the great toe leading to dead bone. A small, hard area had formed several weeks before and sloughed away, leaving a sinus. The sinus had been twice curetted.

The physical examination showed a poorly nourished and poorly developed boy, but not appearing ill. Except for enlarged tonsils and several bad teeth the examination was negative. The heart and palpable blood-vessels seemed normal. There was no disturbance of the sensory nerves. The blood Wassermann was negative and the spinal fluid normal. He gave no history of trauma, of undue exposure to cold or of acute illness. His father and mother, one brother and three sisters were living and well. The toe was amputated and the stump healed soundly.

One year later he returned. He had been well and free from pain until two weeks previously, when he noticed, on the dorsum of the second toe, a large bleb and that the nail had become loose and shortly after the toe had become swollen and red. A conical portion of tissue sloughed out near the tip of the toe, leaving again a sinus leading to bone, exactly similar to the one seen on the great toe. There was little or no pain associated with these changes.

This toe was also amputated and healed promptly. Although the vessels bled freely at both operations, they seemed smaller than normal. The specimen showed the third phalanx nearly absent, only the articular end being present. The microscopical examination of the soft parts showed no evidence of tuberculosis or tumor and no prominent thrombosis. There was much subacute inflammatory tissue lining a tract leading to necrotic bone.

The next year, when sixteen, the patient again came to the hospital. He had been well and free from symptoms until two weeks before his admission. He began, at that time, to have dull pain (somewhat more acute after walking) in the ball of the foot and near the stump of the amputation of the great toe. He had noticed a tender swelling in the left groin. On examination there was a low grade cellulitis over the plantar surface of the foot, having its centre about a sinus situated a few centimetres behind the stump of the great toe. An incision was made through this tissue down to the bone. The wound did not heal. The pain ceased, however, except when the foot was injured; the boy was able to work about a garage.

At the end of another year a few drops of pus were still discharging daily through the sinus. The dorsum of the foot was slightly swollen and somewhat sensitive. The tissue about the sinus on the plantar surface was bluish; the scanty pus discharging from the sinus was foul smelling, as if there was necrosis of the neighboring tissues. There was a large gland in the groin. Sedillot's modification of Pirigoff's amputation was performed, sawing through the os calcis obliquely and turning it up on the tibia, cut slantingly to correspond. No tourniquet was used. The vessels bled freely. The skin was closed without drainage and the stump put up in a plaster-of-Paris bandage. The wound healed by primary union. He has now a strong, end-bearing stump in which the circulation seems normal. The turned-up portion of the os calcis has united firmly to the tibia, partly by bone and partly by strong fibrous union. There is no evidence of lessened calcium deposit in the terminal fragment. (Fig. 11.) The boy uses an artificial foot. When without the foot he walks about his room directly on the stump.

Pathological Report.—Macroscopical Examination: The specimen consists of a left foot, amputated at the ankle, but not including the posterior half of the os calcis. The great and second toes are missing, having been amputated at the metatarso-phalangeal joints. The point of amputation of the second toe has healed over and is covered with thickened, desquamating epithelium. On the ball of the foot, just behind the site of amputation of the great toe, is a half-moon shaped ulcer with a granulating base 2.5 cm. in diameter. The dissected dorsalis pedis artery shows a moderately thickened and white wall, but the lumen appears to be patent throughout. The plantar artery is the same, except that the wall does not appear quite as thick.

Microscopical Examination.—Sections of the larger dorsal and plantar arteries of the amputated foot show the same histological changes. The predominating lesion is an endarteritis, as shown by a connective tissue thickening of the intima. In places this fibrous thickening of the intima is so great as to cause infoldings with a partial occlusion of the lumina. The endothelium is everywhere intact and smooth, and there is no evidence of thrombosis. The media is relatively thickened and in places shows a moderate amount of degeneration of the muscle fibres, recognized by patchy variations in staining. Stains for elastic tissue show the internal elastic lamellæ to be broken and frayed at irregular intervals. The adventitia shows no changes. Cellular infiltration of all the coats is lacking.

Arterioles.—Sections of the arterioles show the same thickening of the intima as is seen in the larger vessels. In the smaller vessels, however, the new fibrous tissue of the intima is relatively greater as compared to the size of the vessel and in many of these the lumina are almost entirely obliterated. The degenerative changes, seen in the media of the larger arteries, are lacking in the arterioles.

Veins.—The veins showed a marked thickening of the intima, due to new connective tissue. The media and adventitia are relatively normal. In the larger veins the thickened intima shows considerable myxomatous degeneration. The endothelium is everywhere intact and smooth and there is no evidence of thrombosis. (Figs. 12, 13, 14 and 15.)

Nerves.—Sections of the smaller nerve bundles show only minor and non-essential changes. The perineurium in places is slightly thickened and hyaline. Many of the fibres are surrounded by a small zone of œdema but degenerative changes of the fibres themselves are not seen.

Soft Tissues.—The soft tissues show only slight pathological changes. In the region of the ulcerated area on the sole of the foot there is œdema of the connective tissue and a moderate degree of round cell infiltration.

In general it can be said that the essential lesions in this case are endarteritis and endophlebitis affecting the larger and smaller vessels alike. The intima is thickened by an increase in connective tissue and in some places, especially in the smaller arterioles, this new tissue is sufficient in amount to occlude almost completely the lumina. The endothelium is everywhere intact and there is no evidence of thrombosis.

Discussion.—The endophlebitis and endarteritis in the amputated foot of this boy are in themselves believed to be sufficiently marked to constitute an adequate cause for the production of the gangrene when trauma or infection are added. While these vascular changes are the ones which are associated with both acute and chronic diseases, the exact etiological factors in this particular case are not at all clear. A positive etiological diagnosis cannot be made and a tentative one can only be arrived at by a process of exclusion.

Clinically, thrombo-angiitis obliterans or Buerger's disease can be eliminated by the age of the patient, his race, and the clinical history and course of the disease. By definition, thrombo-angiitis obliterans is essentially a different process than the one which is seen in the arteries and veins of this boy. Both grossly and microscopically, thrombus formation is the essential lesion. In the acute stages the inflammatory reactions in the wall of the vessel harboring the thrombus are marked and characteristic. In the healed stage the vessel may be completely occluded by a thrombus, or the thrombus may be canalized so as to allow a diminished flow of blood. These changes are simulated in no way by the processes seen in the present case. Therefore, by clinical and histologic means, thrombo-angiitis obliterans can be excluded as a pathological basis for the gangrene in the case under discussion.

The vascular changes due to congenital syphilis may be identical with those seen in this boy. At the same time, the histological changes seen are not characteristic and cannot be differentiated from the changes due to other acute or chronic infections. Therefore the proof for a diagnosis of syphilis must rest on the clinical criteria which in this case are entirely negative. The boy has none of the stigmata of congenital syph-

ilis and there is nothing in the family history to suggest a syphilitic infection. He has a negative blood Wassermann which remains negative after a trial dose of neoarsphenamine. The luetin skin test is negative. The spinal fluid shows a normal cell count and globulin content and the Wassermann reaction is negative. With these negative serological tests and an entirely negative history as regards syphilitic infection of the patient or his parents, a diagnosis of congenital syphilis cannot be made.

Lastly, to be considered as etiological factors are the circulating toxic agents of the infectious diseases. The widespread and uniform distribution of the vascular lesions in the amputated foot of this patient strongly suggest a direct toxic injury to the intima. The repair of this injury with new fibrous tissue has been sufficient, in the smaller arteries at least, to almost occlude the lumina. Therefore, by the process of exclusion and in the absence of other more definite etiological factors, we are forced to conclude that the vascular changes, with the resulting gangrene of the toes, are probably dependent on the injury due to circulating toxins or microörganisms of past infections.

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NON-UNION OF FRACTURES

AN EXPERIMENTAL AND CLINICAL STUDY

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The following observations present instructive information regarding the anatomical conditions found in non-union of fractures and the abnormal healing processes responsible for these conditions. The subject of non-union of fractures has been studied largely from the standpoint of surgical therapy.

When we examine the literature for causes of ununited fracture, we find a variety of conditions, both general and local, which have been considered etiologic factors. In fact it appears that any systemic disease which the patient may have had at the time of fracture has been deemed a cause of failure of union, either through a specific toxin, as in syphilis, or through deterioration of health, as in diabetes, nephritis, anæmia, or through dysfunction of the endocrine system with deficiency of calcium metabolism.

Of the local conditions assigned as causes of non-union we find defective innervation, disturbance of the blood supply of one or both fragments through injury to the nutrient artery, imperfect immobilization, too perfect and prolonged immobilization, too great separation of the fragments, interposition of soft parts, infection with excessive suppuration, osteosclerosis of the ends of the fragments, tumors, lack of osteogenetic power and suspended vitality.

It soon became apparent in the study of our cases that all of the general and most of the local causes given as factors in the production of non-union could be ruled out, for in a series of forty-two cases of non-union all but two patients were robust, healthy men of middle age, who at the time of fracture were engaged in hard manual labor or were performing vigorous exercise. This agrees with the observations of surgeons in general, that failure of bony union following fracture occurs more often in the prime of life than at any other time.

The exceptions in our series were two: a boy, six years of age, who had had extensive suppuration following open reduction of a fracture of the radius; and a young woman, twenty-two years of age, with a moderately severe case of diabetes. In these two patients operations were performed and bony union occurred in the usual time.

There are two local conditions which all agree are important factors in the production of non-union. First, we know from clinical experience and from experimental study, that the interposition of soft parts will cause non-union; and secondly, that wide separation of the fragments by the original vulnerating force, by gravity, by muscular contraction, or by loss of cortical

bone in compound fractures may be followed by fibrous union. The effect of gravity is best seen in fracture of the mid-portion of the shaft of the humerus in which the weight of the lower portion of the arm and forearm tends to separate the fragments. The effect of muscular contraction is observed in fracture of the patella, the olecranon process and in the avulsion of an apophysis in which cases fibrous union is the rule, if surgical reposition and fixation of the fragments are not secured.

As we occasionally see fracture of each of two-paired bones, followed by firm bony union in one and fibrous union in the other, or two or more fractures at different levels of the shaft of one bone in which all but one heal by bony union, it is reasonable to suppose that failure of osseous union is due to some local condition.

At the beginning of our study of ununited fracture it became evident that a clear conception of the histological processes occurring in the repair of a simple fracture was essential for the appreciation of the variations in these processes which give rise to non-union. It was also obvious that there was a decided lack of knowledge of the exact anatomical conditions present in cases of non-union.

It is known that the fragments are united by a bond of fibrous tissue, and as fibrous tissue is supposed to represent a stage through which the processes of repair of a fracture commonly pass, failure of ossification of the bond results in non-union. Just why ossification fails in these cases was not clear and the use of such expressions as lack of osteogenetic power and suspended vitality does not bring us any nearer the solution of the problem.

Bone possesses an extraordinary power of self-repair. This is not surprising when its mesoblastic origin is considered, for all mesoblastic tissues of the body possess unusual power of repair. It is a fact that osteogenesis does not progress at the same rate in all individuals nor in all bones of the same individual and it is easy to conceive that osteogenesis may differ in the same bone of an individual at different times.

But granting that the processes of repair are much more rapid in certain individuals than in others, and providing the various general and most of the local causes considered as factors in the production of non-union are absent, bony union ought to occur in a fracture of a long bone of a healthy animal in a reasonable time, unless there are some underlying anatomical conditions which prevent this.

In collaboration with Dr. Frank E. Blaisdell, the writer produced a series of simple fractures in kittens. By simple fracture is meant one in which there has been solution of continuity of the cortical bone without displacement of the fragments or with reposition of the fragments as near as possible to the normal position, and with a minimum amount of damage to the ends of the fragments and the surrounding soft parts, especially the periosteum.

Under ether anæsthesia the right humerus was bent across the thum, in most instances the bone fracturing with an audible snap. The animals were sacrificed with chloroform at intervals of twelve hours to thirty-four days

and the specimens studied radiographically, grossly and microscopically. Our observations included first, the immediate changes in the bone and surrounding soft parts which followed fracture and resulted from trauma; and secondly, the changes constituting the inflammatory reaction which result in a repair of fracture.

The different tissues of bone, namely the periosteum, cortical bone and medullary tissue were studied for the purpose of determining the precise rôle played by these in the reparative process. These tissues were also studied in animals of the same species at different ages and observations were made on the periosteum and cortical bone of children and adults during operation.

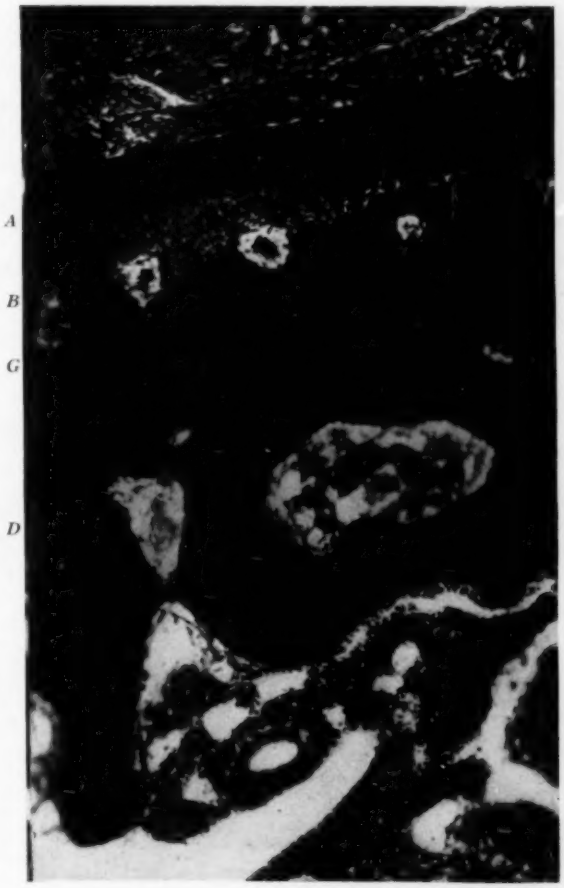


FIG. 1.—Transverse section of tibia of six months' human fetus showing: A—Fibrous layer of periosteum. B—Layers of osteal fibroblasts. G—Cortical bone. D—Haversian Canal with osteal fibroblasts depositing new bone.

A study of these specimens shows the following: The periosteum of the growing bone of a young animal or child is a strong, thick, elastic and highly vascular membrane, firmly attached to the bone in the region of the epiphyseal lines, but elsewhere more loosely attached through the medium of a delicate areolar tissue, in the interstices of which are several layers of large cells, the osteal fibroblasts. The blood-vessels of the periosteum subdivide rapidly before entering the cortical bone. This vascular supply is most important. The membrane is easily stripped up from the cortical bone. If we compare this membrane with the periosteum in the adult human or experimental animal in which the bone has reached its maximum growth, we find that the latter membrane is relatively and often absolutely thinner, less elastic, less vascular and more firmly adherent to the cortical bone. Osteal fibroblasts may be present at intervals as a single layer; they may be difficult to find, or they are absent. Often the adult periosteal membrane is found to strip up from the cortical bone with difficulty and it may be found lacerated in part or in whole flush with the fracture line.

Examination of the cortical bone shows considerable variation in thickness and density in the human and experimental animals at different ages. The cortical bone of a young, growing animal is thin, the haversian canals are large and filled with a delicate reticular tissue supporting blood-vessels. Along the walls of these canals many osteal fibroblasts are seen. In the adult, the cortical bone is thicker and more dense, the haversian canals relatively smaller and the osteal fibroblasts are much less in evidence.

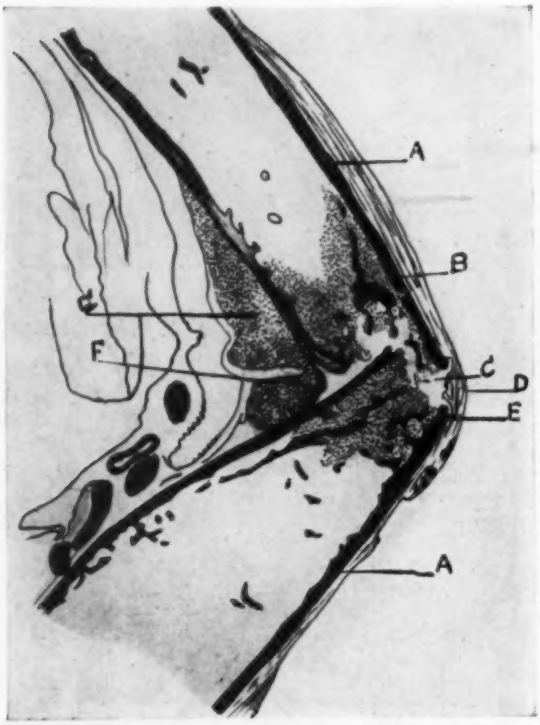


FIG. 2.—Camera lucida drawing of longitudinal section at site of fracture of humerus of kitten showing: A—Cortical bone. B—Periosteum, continuous on side of angulation and ruptured on opposite side, E. C—Area of hæmorrhage within medullary portion of bone. D—Muscle drawn tightly over area of laceration of periosteum. F—Periosteum and thin layer of cortical bone. G—Area of hæmorrhage external to periosteum.

Bones of the young frequently bend and buckle, and in experimental specimens from kittens, the lamellæ of the cortical bone are seen to slide on each other and the cortex bends, fissures, or fragments. In the adult, the thick, dense cortical bone often fractures in one plane or fragments much as a cast-iron rod breaks under strain. The medullary tissues vary with age. In the bone of the young growing animal the marrow is lymphoid and quite vascular and the bone trabeculæ are surrounded with one or more layers of osteal fibroblasts. In the adult animal the marrow is fatty, less vascular and osteal fibroblasts are fewer in number or often absent from the surface of the trabeculæ.

A study of our experimental specimens at various stages of the reparative process of a simple fracture shows the following:

With solution of the continuity of the cortical bone hæmorrhage occurs from the lacerated vessels of the periosteum, haversian canals of the cortical bone, and the marrow. The blood extravasates, beneath the periosteum, about the fractured ends of the cortical bone and for varying distances into the medullary portion of each fragment. With laceration of the periosteum, blood finds its way into the surrounding soft parts. The extent of hæmorrhage will depend upon the vascularity of the periosteum and marrow and upon the amount of separation of the periosteum from the cortical bone, which determines the degree of resistance offered to suffusion.

Blood coagulates and seals the lacerated vessels. Fibrin is deposited

beneath the periosteum, about the ends of the fragments and in the medulla. Fibrin is a natural stimulus to fibroblastic proliferation. In these cases, when leukocytes are not present or when they are not attracted by injurious agents, fibrin is not dissolved and acts as a bridge between the fragments and exerts a specific attraction for fibroblasts. The cells begin to proliferate within a few hours, invade the fibrin mesh-work and rapidly replace it.

Fibroblastic proliferation is accompanied or probably preceded by the proliferation of vascular endothelium in the form of fine capillary buds. As early as the second day, end buds from the vessels of the periosteum and medulla can be observed about the periphery of the clot. These invade the clot and gradually replace it by a mass of vascular, œdematous granulation tissue consisting for the most part of anastomosing end buds and capillary loops, the procallus granulation tissue.

This procallus granulation tissue is well developed at the end of the first week, both in the medulla, where as fibrous marrow it has replaced the lymphoid marrow, and in the subperiosteal space. These procallus granulation masses fuse and reëstablish vascular communication between the fragments.

Osteal fibroblasts which are numerous on the surface of the cortical bone, on the surface of the trabeculæ and along the walls of the haversian canals in these young animals, proliferate along the vessels of the procallus granulation tissue, and osteoid material and cartilage are deposited. Ossification proceeds on the walls of the blood-vessels, and cylinders of new bone are laid down which later form the lamellæ of the cortical bone and the trabeculæ of the medulla.

It appears that pressure on the developing calluses plays an important part in the formation of cartilage. This pressure may be due to contact of the dense cortical bone with the medullary procallus granulations or to the overlying periosteum, which may be stretched and tense. The medullary procallus granulations often undergo ossification without an intermediate cartilaginous stage. In the specimens in which cartilage was present in the medulla of these bones there was always considerable lateral displacement of the fragments so that the cortical bone of one fragment lay in contact with the medulla of the other.

With the lifting up of the periosteum and the formation of blood clot in the subperiosteal and medullary areas, the cortical bone for varying distances on either side of the fracture line is deprived of its blood supply. Bone cells die and the lacunæ rapidly become vacant.

Bone is different from all other tissue in having an abundant intercellular substance in which lime salts are deposited. If the bone cells are killed, this intercellular substance immediately becomes a foreign body which requires removal. The necrotic or deal cortical bone becomes irregular on its surface by cellular and vascular erosion and the haversian canals enlarged and irregular. As the haversian canals become enlarged and irregular in

outline, new bone is deposited on their walls, and this new bone is continuous on the external and internal surface of the cortex with the subperiosteal and medullary calluses. A sharp line of demarcation is clearly seen between the dead bone and the newly developed osseous callus.

Rarefaction of the dead bone continues and new bone is deposited until all of the dead bone has been replaced. With the restoration of function, those portions of the subperiosteal and medullary calluses which lie outside the lines of pressure are gradually absorbed, while those portions of the calluses which lie within the lines of pressure are gradually thickened (Wolff's Law). As the medullary osseous callus disappears, the marrow again becomes lymphoid in character and healing is complete.

From these experiments it is seen that of the three tissues—periosteum, medullary tissue, and cortical bone—the periosteum is the most important. Leaving out of consideration the osteogenetic power of the periosteum, this tissue serves two very important functions in the healing of fractures: (1) without complete laceration, the periosteum serves as a bridge between the fragments which prevents their separation; and (2) it serves as a limiting membrane to confine the blood, and hence limit the clot in which the procallus granulation tissue develops.

Successful union is dependent upon the establishment of vascular communication between the procallus granulation tissue of the fragments. When contact of the fragments leaves no room for an appreciable clot, or what amounts to the same thing, when the apposition of the fragments is perfect, so that the clot is infinitesimal, healing by osseous union is almost certain to occur. Under these conditions, vascular communication is rapidly established between the fragments and healing may be said to occur per primam. This condition obtains in impacted fractures.

In all experimental specimens in which the periosteum remained intact but was lifted off the cortical bone, the subperiosteal callus appeared early and was the most important factor in healing by osseous union. In the cases in which the periosteum was lacerated flush with the fracture line, but was lifted up for a short distance on either fragment, subperiosteal callus developed, and resulted in an increase in the diameter of the end of the fragment. When the periosteum was retracted for a short distance from the fracture line, the end of the fragment became smaller by cellular and vascular erosion of the necrotic bone. When the periosteum remained adherent to the cortical bone at the line of fracture, no subperiosteal callus appeared, and the diameter of the end of the fragment remained unchanged.

Following a fracture with hæmorrhage into the medulla, the lymphoid marrow is rapidly replaced by fibrous marrow. This delicate, highly vascular, and œdematous procallus granulation tissue is gradually replaced by osteoid and cartilaginous callus formed by osteal fibroblasts proliferating along the walls of the capillaries. Bone trabeculæ rapidly make their appearance along the inner surface of the cortical bone, bridge across the medul-

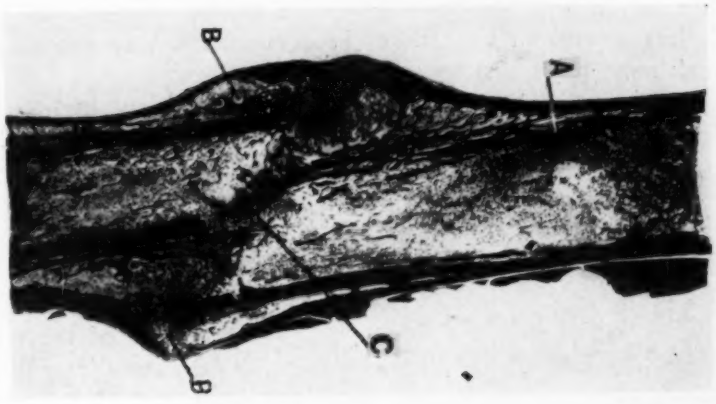


FIG. 3.—Healing of fracture of humerus of kitten showing: A—Original cortical bone undergoing process of rarefaction. B—Subperiosteal osseous callus. C—Medullary osseous callus uniting fragments.

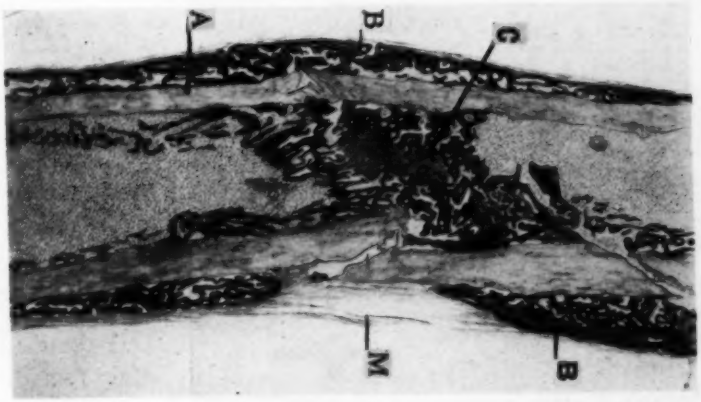


FIG. 4.—Healing of experimentally produced fracture of humerus of kitten showing: A—Original cortical bone. B—Subperiosteal osseous callus. C—Medullary or internal osseous callus. *Note*—M; where the periosteum has been lacerated, and has retracted the cortical bone, is covered with fibrous tissue and subperiosteal osseous callus is absent. Above and below M, where the periosteum has been lifted up from the cortical bone, subperiosteal osseous callus has formed which has increased the diameter of the bone at these levels.

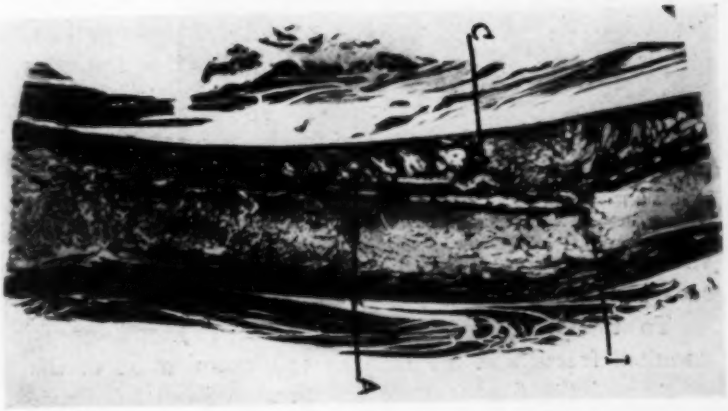


FIG. 5.—Healing of experimentally produced fracture of humerus of kitten showing: A—Original cortical bone undergoing rarefaction by cellular and vascular erosion. C—Subperiosteal osseous callus on side of angulation, where periosteum has been lifted up from the cortical bone; note absence of subperiosteal callus on side opposite angulation where periosteum has remained adherent to cortical bone. L—Remains of medullary or internal osseous callus with lymphoid marrow above and below.

lary space as the internal or medullary osseous callus and finally across the line of fracture, thus uniting the fragments. The medullary osseous callus is less in amount and slower in development than the subperiosteal callus and hence plays a rôle second in importance.

The cortical bone assumes a passive rôle in the healing process. Varying amounts of cortical bone on either side of the fracture line become necrotic. Near the ends of the fragments, bone cells have disappeared; a little farther away they stain poorly and are undergoing autolysis. The surface of the necrotic bone becomes irregular from vascular and cellular erosion.

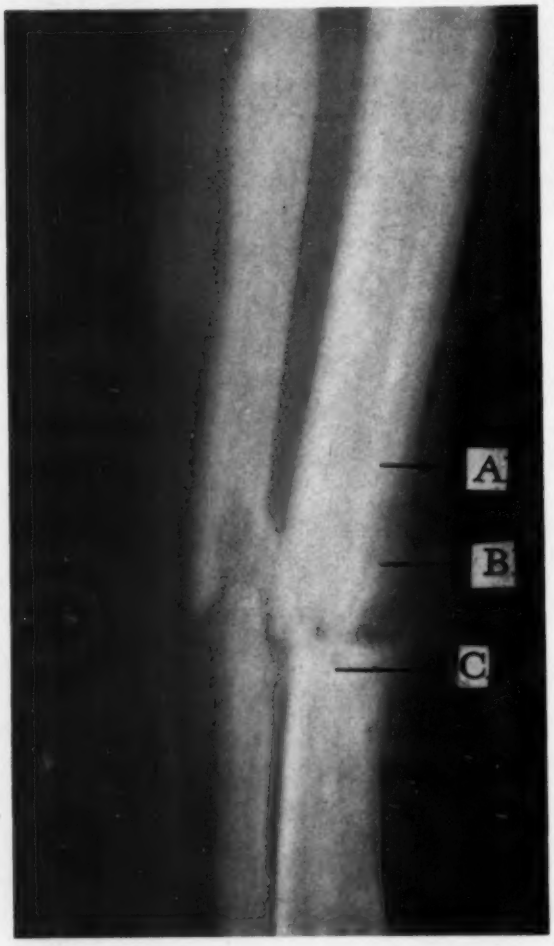


FIG. 6.—Radiogram of ununited fracture of tibia showing: A—Thick cortical bone. B—Subperiosteal osseous callus, and C—medullary callus forming bone buttress. Note increase in diameter of upper end of lower fragment.

The circulation is reëstablished rapidly by the ingrowth of new blood-vessels of the procallus granulations; the haversian canals become enlarged and irregular. Osteal fibroblasts surrounding these vessels deposit new bone on the walls of the canals and a sharp line of demarcation between living and dead bone is clearly seen. This process continues until the dead bone is completely replaced. The so-called intermediate callus is absent and any callus between the cortical ends of the fragments develops from the sub-periosteal or medullary calluses.

Having studied the processes of repair of a simple fracture which result in bony union, our next problem was to determine if possible the variations in these processes which result in non-union and the causes of such variations.

To this end our studies included: (1) radiographic examination of ununited fracture in the human; (2) examination of the ends of the fragments and the fibrous bond at operation, and microscopic study of specimens removed at operation; (3) the experimental production of non-union with microscopic examination of specimens and the comparison of these

with cases from the human; (4) efforts to secure osseous union in cases of experimentally produced non-union, and (5) the application of the knowledge thus gained to the surgical treatment of non-union in the human.

Radiographic examinations of ununited fractures in the human showed a thick dense cortex, the development of a medullary osseous callus filling the ends of the fragments and forming a bone buttress; an increase in the diameter of the end of one or both fragments with an occasional isolated nodule of increased density in the fibrous bond; or a decrease in the end of one or rarely both fragments, or convexity of the end of one fragment, usually the upper, and concavity of the end of the other, usually the lower, with a cleft between the two.

FIG. 7.—United fracture of tibia and fibula in human. F—Fibula fragments. Note increase in diameter of upper end of lower fragment. T—Tibial fragments with medullary osseous callus. H—Fibrous bond, the fibres of which are directed parallel to ends of fragment. L—Fibro-cartilage being replaced by ingrowth of vessels from marrow spaces of tibial fragments. Note serrations of bone ends at L, and bone buttress above and below H in fibular fragments.

Observations of the fibrous bond at the time of operation, and histologic examination of tissue removed at operation showed three distinct types of non-osseous union: (1) a firm fibrous union, (2) a loose fibrous union with or without clefts between bundles of dense collagen fibrils, and (3) a definite pseudarthrosis, with cartilage and synovial membrane.

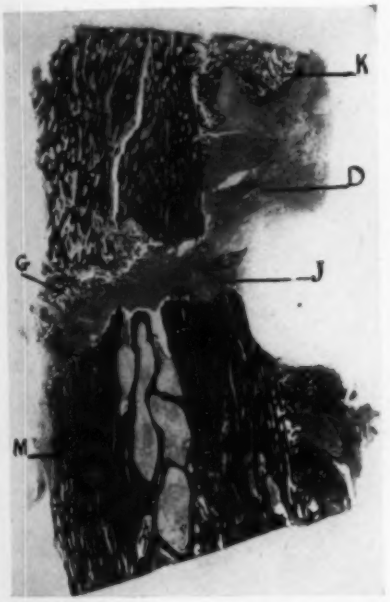


FIG. 8.—Ununited fracture of tibia in human showing: M—Thick dense cortex of fragment. J—Fibrous bond, the fibres of which lie in plane parallel to ends of fragments. G—New formed trabeculæ of medullary pro-callus granulation. D—Dense fibrous tissue. K—Subperiosteal osseous callus. Note cortical bone beneath fibrous bond at J shows no new bone, while further down the cortex of the lower fragment where the periosteum has been lifted up subperiosteal osseous callus is present.

1. *Firm Fibrous Union.*—The fragments were usually in good alignment with slight separation. The ends of the fragments were either of normal diameter or more often one was of normal, the other of increased diameter, and the medullary portions were occupied by bone. In most instances a distinct bone buttress separated the marrow spaces from the fibrous bond; in others the surfaces were finely serrated and the marrow spaces were open. In this variety a fibrocartilage caps the ends of the fragments. The bond consists of a dense avascular fibrous tissue, the collagen bundles of which are directed for the most part parallel to the ends of the fragments

or at right angles to the long axis of the bone. These fibres can be traced inward from the periosteum. The outermost fibres unite the periosteum of the fragments and run in a direction parallel to the long axis of the bone. Often there is enough bone production in each fragment to bridge the gap.

2. *Loose Fibrous Union.*—In case of loose fibrous union the ends of the fragments present much the same appearance as cases of firm fibrous union, with the exception that the ends of the fragments are serrated and a bone buttress separates the marrow spaces from the fibrous bond. The fibres of the dense avascular fibrous bond run largely in a direction parallel to the long axis of the fragments and are united to the bony serrations. In some specimens clefts appear in the fibrous tissue, the walls of which are quite irregular and the tissue is ragged and stains poorly.

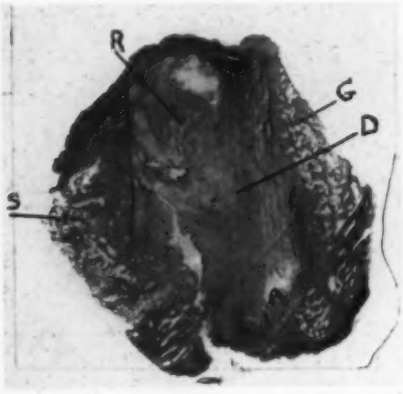


FIG. 9.—Ununited fracture of tibia in human with loose fibrous bond showing: S—Fragment. D—Fibrous bond, the fibres of which run for the most part parallel to the long axis of the fragments. G—New bone formed from medullary pro-callus granulation tissue. R—Island of new-formed bone in fibrous bond.

3. *Pseudarthritis.*—In this case the apposing surfaces of the fragments are irregularly concavo-convex. The concavity is formed by growth of bone at the periphery, there often being more bone developed than is necessary to bridge the defect. The trabeculæ of the ends of the fragments are considerably thickened, a bone buttress is formed and the apposing surfaces are covered with fibrocartilage. At the periphery the bones are united by fibrous tissue, which forms the capsule of the new joint. In some areas synovial membrane is present.

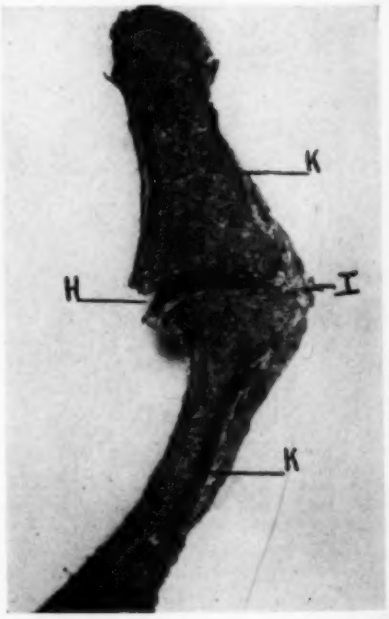


FIG. 10.—Pseudarthrosis of clavicle of human following fracture to show: K—Fragments. H—Joint space. I—Capsule of new joint. Note concavo-convex outline of the joint surface and thickening of ends of fragments. There has been sufficient bone production to bridge the gap.

It was apparent from the examination of these specimens that there was one factor common to all and that was a separation of the fragments. The degree of separation varied from one-eighth to one-half inch or more. In transverse fracture of the mid-portion of the shaft of the humerus, the separation of the fragments was greatest. In oblique fractures of the tibia separation was of a less degree but was still apparent. *Separation of fragments can occur only by a stretching or*

laceration of the periosteum. As the periosteum in adults is relatively thin and less elastic than in the young, it is more apt to tear than to stretch.

Observations made during open reduction of fractures in which radiographic examination revealed a thick, dense cortical bone, with moderate separation of fragments, showed a complete laceration of the periosteum. In several cases we were able to pass a probe between the fragments and demonstrate a complete absence of periosteal continuity. In some instances laceration of the periosteum occurred flush with the line of fracture with or without slight retraction. Where retraction occurred, the periosteum had been detached from the fragments for a slight distance on either side of the fracture line. In other cases the periosteum had been stretched and detached from the cortical bone and ruptured on one or the other side of the fracture line so that the end of one fragment retained its periosteal sheath, while the other was denuded for a short distance.

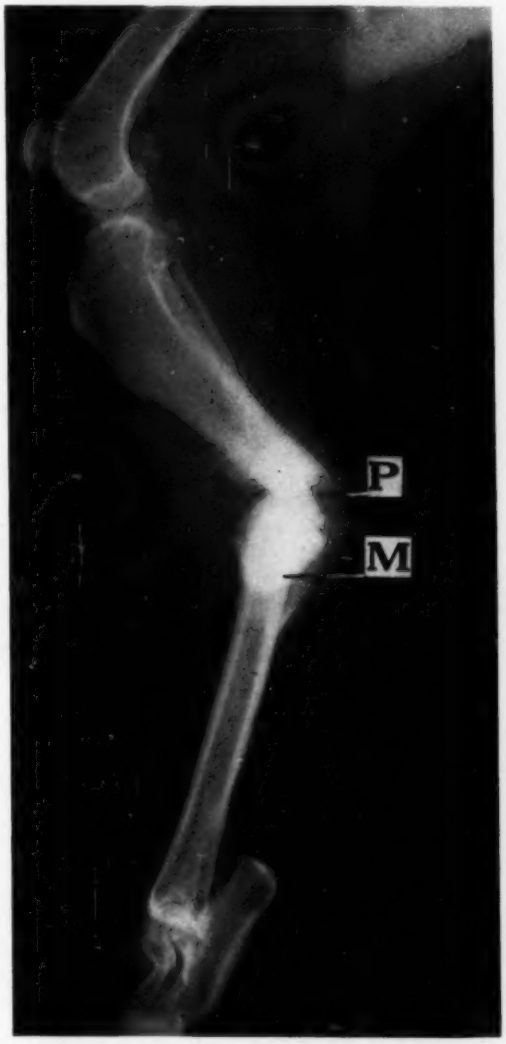


FIG. 11.—Experimentally produced ununited fracture of the tibia of dog. P—Area of fibrous bond. M—Upper end of lower fragment showing original cortical bone, and increased diameter of fragment in this area due to formation of new bone.

The importance of laceration of the periosteum and separation of the fragments is seen in fracture of the patella and olecranon. Even with slight separation fibrous union is the rule in these cases and it is only after suture of the fibroperiosteum and the lateral aponeurotic expansions that bony union is most likely to occur.

The separation of fragments results from (1) the original vulnerating force producing fracture, (2) gravity, as for example, the weight of the lower arm and forearm in cases of fracture of the mid-portion of the shaft of the humerus, and (3) muscle pull as in fracture of the patella and olecranon process. Even the application of a Lane plate to the irregular surfaces of fragments may cause separation on the side opposite the plate. It

was found that non-union was not uncommon after plating and the use of plates has been warned against by many writers.

By producing solution of continuity of the cortical bone without lifting up the periosteum we sought to eliminate to a large extent the subperiosteal callus which we have seen is of such importance in the healing of simple fractures. Healing would then depend upon the more tardy and less abundant medullary callus. We therefore incised the periosteum of the mid-portion of the shaft of the tibia of the dog to avoid gross injury, especially to avoid lifting it off the cortical bone and then sawed through the latter with a fine saw. As there is a tibio-fibular synostosis in the dog, the fibula prevented separation of the tibial fragments and we secured bony union in some of our specimens. With fracture of the fibula, however, the weight of the foot and lower portion of the leg was sufficient to cause separation of the fragments, even though the extremity was immobilized in a plaster spica well padded with sheet wadding.

FIG. 12.—Experimentally produced ununited fracture in the tibia of dog showing: A—Sclerosed ends of fragments, and D—fibrous bond, the fibres of which extend inward from the periosteum in a direction parallel to the surfaces of the fractured ends or at right angle to the long axis of fragments.

We have seen that bony union requires the establishment of a vascular communication between the fragments, or a fusion of the procallus granulations. As has been said, the more accurate the apposition, the more certain is healing by osseous union to occur. If the fragments are not maintained in close apposition, but are separated even slightly, the clot between the fragments is greater in amount and there is an additional factor in the reparative process tending to delay or even to stop completely bony healing. This is the ingrowth of granulation tissue from the periosteum. This hardier connective tissue reacts to injury by proliferation, invades and organizes the clot between the fragments with greater rapidity than the more tardy granulations developing from the vessels of the marrow spaces. It forms a limiting membrane, which prevents fusion of the vessels of the medullary procallus granulations as effectively as an interposed piece of fascia or muscle.

The two types of granulations are easily distinguishable microscopically. That springing from the capillaries of the marrow spaces is delicate, highly vascular and œdematous, with fine collagen fibrils similar to the fibrous marrow from which it springs; while that growing in from the periosteum is

dense, avascular with large bundles of collagen fibres compactly united like the fibrous periosteum from which it develops. At times the rate of growth of these two granulation masses appears to be about equal, so that a combination or intertwining of the two can be seen. Osteal fibroblasts from the marrow and haversian canals of the cortical bone proliferate along the capillaries of the medullary procallus granulations and form cartilage and bone. The final result of the reparative process will depend upon which of the two granulation masses gets the upper hand. If the medullary procallus granulation masses win, vascular communication between the fragments results, and bony union occurs. If there is a tie, irregular bony projections appear about the ends of the fragments and isolated nodules, or islands of bone develop in the fibrous bond, or union occurs over a portion of the extent of the fractured surfaces only. If the dense, avascular tissue from the periosteum gets the upper hand, it seems to choke the more delicate and vascular granulations from the marrow spaces and prevents their fusion in a manner analogous to that which occurs in a so-called amputation neuroma, in which we see the axis cylinders of the proximal segment of the injured nerve twisted and compressed in every direction. There appears to be sufficient growth of axons in the neuroma to bridge the defect, but they cannot get across.

Likewise in fracture, there seems to be no failure of osteogenesis in most of the specimens which have failed to unite by bony union, for long spurs of bone, more than sufficient to bridge the space, are often seen extending from one or both fragments. The ingrowth of dense fibrous tissue from the periosteum has acted as a limiting membrane to prevent fusion of the medullary granulations.

Coincidently with the ingrowth of fibrous tissue from the periosteum, osteal fibroblasts proliferate along the vessels of the medullary procallus granulations and deposit bone which eventually plugs the medullary portion of each major fragment for a short distance from the end. In the earlier stages the junction of bone and fibrous bond is irregular, the bone ends are serrated and one sees active bone formation going on here with fibrous marrow between the serrations. Later we find a well marked bone buttress extending across the bone ends which separates and shuts off the marrow spaces from the fibrous bond. As the function of weight bearing is not resumed, because of instability, the medullary osseous callus does not disappear as in the healed fracture, but persists giving rise to the eburnated end of one or both fragments.

Where the periosteum is separated from the end of the fragment but remains as a sheath, a subperiosteal osseous callus forms which increases the diameter of the bone end. Where the end of the fragment is denuded, the outer layers of the bone become necrotic, granulation tissue surrounds it, the bone is gradually absorbed and becomes more or less conical in shape surrounded by scar tissue.

Function plays an important rôle in determining the type of non-union.

In paired bones, such as the tibia and fibula or radius and ulna, where only one bone is fractured, but the fragments are not in contact, its fellow acts to prevent wide separation. Here the bundles of collagen fibres of the bond run for the most part parallel to the fractured surfaces. The same picture is seen in cases of fracture of the two bones where immobilization has prevented separation or rather where tension has not tended to separate the fragments.

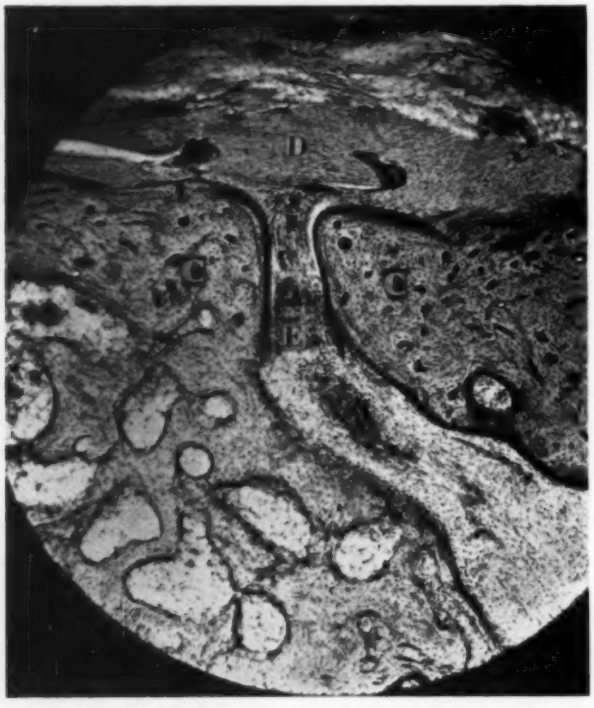


FIG. 13.—Drill hole in anterior surface of patella of dog showing: C—Patella. D—Fibro-periosteum and E—fibrous tissue ingrowth plugging hole. Note also bone buttress separating fibrous plug from marrow spaces.

To demonstrate the effect of the absence of pressure and tension on the granulation tissue developing from the periosteum the following experiment was performed.

The anterior surface of the patella is covered by a thick fibroperiosteum. Beneath this the cortical bone is dense. If we drill a hole through half the thickness of the patella from the anterior surface, this becomes filled with dense fibrous tissue, continuous with the periosteum, the fibres of which run in a direction parallel to the long axis of the hole. The more slowly developing granulations from the marrow spaces are prevented from fusing by this plug of dense fibrous tissue and new bone is deposited about the plug which forms a distinct wall. The arrangement of the cells and fibrils parallel to the long axis of the drill hole can best be explained by the absence of pressure and tension.

Where gravity or muscular contraction produces tension on the developing granulations the fibroblasts respond to this by the production of an abundance of fibrous tissue, the cells and fibres of which are arranged in the lines of tension and a fibrous bond similar in structure to a tendon is formed. We see this type of bond in cases of fracture of the patella and olecranon process, in which the fragments have been insecurely placed in position by suture or nail, but which have been separated gradually by muscle pull. In the dog this type is easily produced in the tibia by padding the plaster spica with sheet wadding. As the animal jumps about on three legs the lower fragment tends to be pulled away from the upper by gravity. In

this type the uniting fibres run for the most part parallel to the long axis of the fragments, a buttress of bone separates the marrow spaces from the fibrous bond, the bone ends are more or less serrated and the uniting dense, avascular fibrous tissue bundles, tendon-like in structure, merge into the teeth of bone. This is observed in cases of non-union following fracture of the mid-portion of the humerus in the human, where the weight of the lower portion of the arm and forearm has gradually separated the fragments.

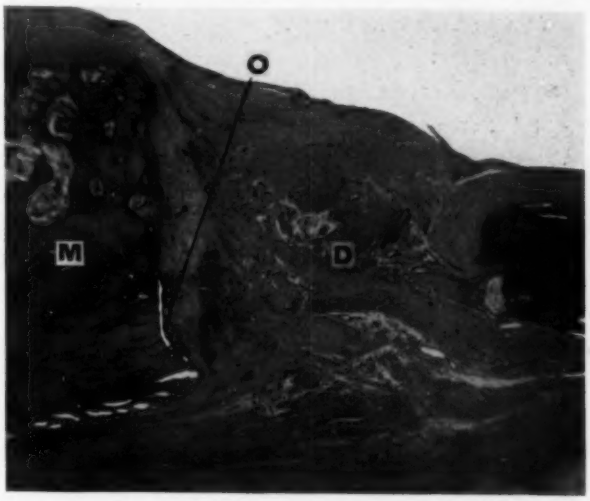


FIG. 14.—Experimentally produced fracture of patella of dog with suture of fibro-periosteum, separation of fragments by muscle pull. M—Fragment of patella. O—Medullary pro-callus granulation tissue, and D—dense fibrous tissue bond.

The difference between the medullary and periosteal types of granulations and the effect of tension during the developing of these is easily demonstrated experimentally in case of fracture of the patella. None of the ordinary methods used in holding the fragments of a fractured patella together are sufficient to prevent separation by the pull of the quadriceps extensor cruris muscle in experimental animals. If the patella is sawed transversely in its mid-portion and the fragments are brought together by suture of the fibro-periosteum or by circular suture with wire, the steady pull of the muscles gradually separates the fragments, the sutures holding for a short time only. Granulation tissue develops from the marrow spaces of the patellar fragments. This is delicate, œdematous and highly vascular with fine collagen fibrils. Osteal fibroblasts from the marrow spaces invade this medullary procallus granulation tissue and produce bone trabeculæ. Granulation tissue develops also from the periosteum. This gives rise to a dense and much less vascular fibrous tissue which is similar to the tissue from which it springs. Because of tension the long axes of the trabeculæ run parallel to the lines of tension so that the bone ends are serrated. The fibrous tissue developing from the periosteal granulations and uniting the fragments respond to tension by the formation of dense fibrous tissue, the fibroblasts and collagen bundles

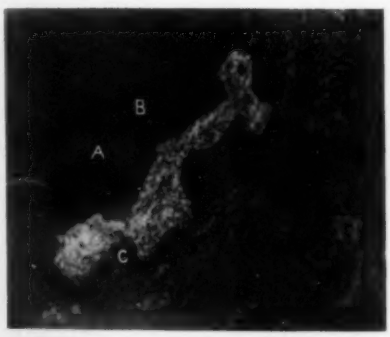


FIG. 15.—Fragment of experimentally produced fracture of the patella in dog showing: A—Fragment. B—New bone trabecula developing in medullary pro-callus granulation tissue C.

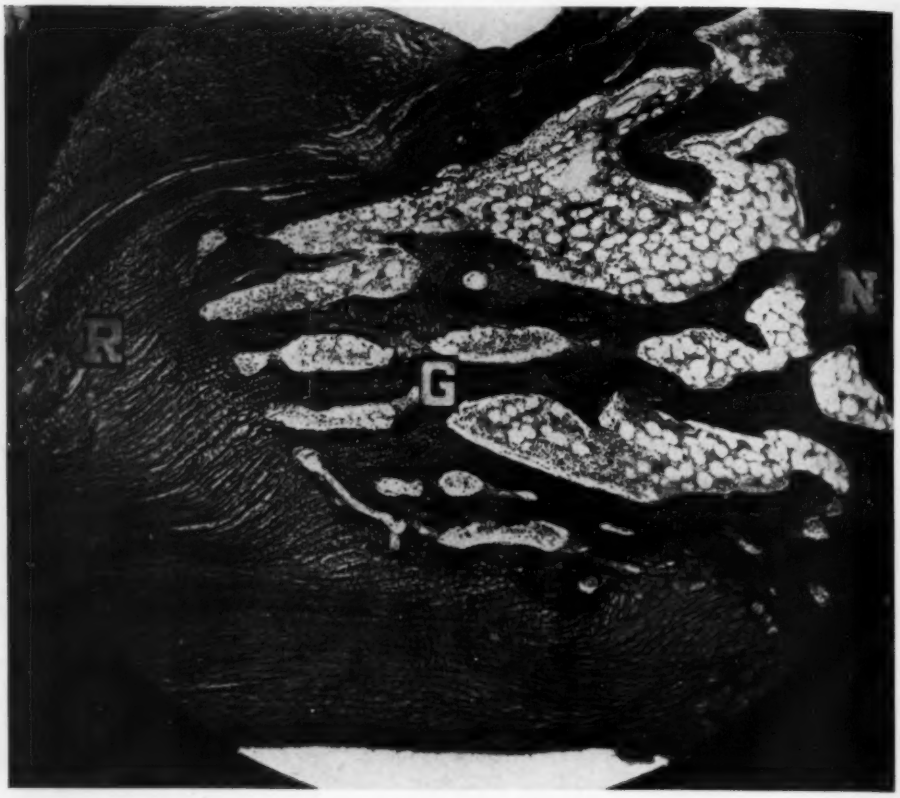


FIG. 16.—Fragment of experimentally produced fracture of dog showing: N—Original fragment. G—New bone trabeculæ developed from medullary pro-callus granulations. R—Fibrous bond. Note—Trabeculæ and fibres of bond extend in direction parallel to lines of tension. Serrations of end of fragment.

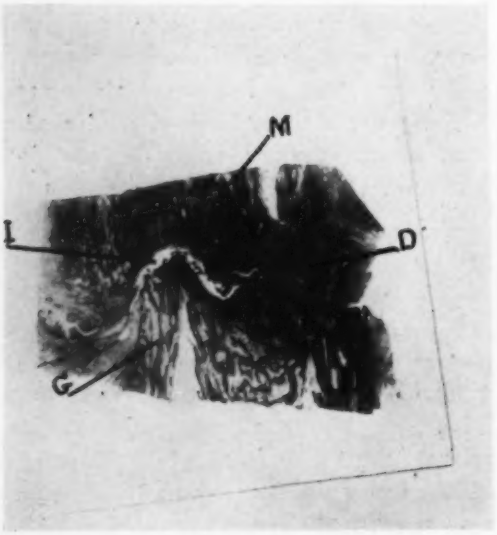


FIG. 17.—Old ununited fracture of tibia in the human showing: M—Osseous medullary plug. D—Fibrous bond. I—Cleft in fibrous bond, filled with débris, the result of necrosis of the fibrous tissue of the bond due to pressure and motion.

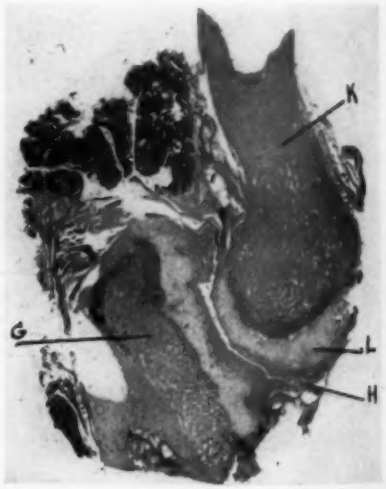


FIG. 18.—Experimentally produced pseudarthrosis in tibia of dog showing: K—Upper fragment. L—Fibrocartilage. G—New bone developed from medullary pro-callus granulations of lower fragment covered with cartilage, and H—joint space.

of which are arranged in the lines of tension and form a strong tendon-like structure.

In the third type of non-union there are irregular clefts in the fibrous bone or a well-defined joint cavity with cartilage capping the ends of the fragments. The fragments are end to end, end to side, or side to side, and the medullary portions of the ends are plugged with bone trabeculæ. In some of the specimens the apposing surfaces of the fragments are quite irregular and serrated and one sees either bare bone or bone covered with necrotic and poorly-staining fibrous tissue. In other specimens the surfaces are irregular but smooth and in these there are areas of fibrocartilage undergoing ossification and areas in which the bone is irregular and serrated with fibrous tissue continuous with the serrations. In this type little motion is present due to the irregularities of the bone ends.

In other specimens a well-defined joint cavity is present between the apposing surfaces of the fragments. The end of the upper fragment is usually convex, while that of the lower fragment is concave. The concavity is formed by growth of bone at the periphery and in some specimens more bone has developed than is required to bridge the defect. In this type the medullary portion of the ends of the fragments is filled with bone trabeculæ of the internal callus, a bone buttress extends across with fibrocartilage. At the periphery the fragments are united by fibrous tissue continuous with the periosteum, on the under surfaces of which a tissue resembling synovial membrane is seen. From the study of our experimental specimens the manner in which these different types of pseudarthrosis are formed appears to be as follows:

The fibrous bond having been formed and the medullary calluses having ossified, the limb is mobilized by the removal of the spica, and restoration of function, particularly weight bearing is resumed. This weight bearing causes the uniting fibrous tissue to be compressed. If, in addition, there are sliding movements between the fragments, the collagen bundles are separated, their fibres are ground and torn, and irregular slits or clefts with ragged walls appear. Continued compression causes necrosis of the fibrous tissue as is shown by its structureless appearance and staining reaction and the necrotic material is gradually absorbed or remains in the clefts as débris.

If mobilization and weight bearing or pressure occur after the fibrous bond has formed, but before the medullary calluses have completely ossified, the medullary calluses of the ends of the fragments are transformed into fibrocartilage. Beneath the cartilage a bone buttress appears separating the new cartilage from the marrow spaces. In portions of the pseudarthrosis where there is motion without pressure we often find a tissue resembling synovial membrane. To show the effect of motion and pressure on the granulations developing from the marrow spaces the following experiment was performed: The patella is normally subjected to pressure as well as to tension. Its posterior surface is covered by articular cartilage. If a hole is drilled in the posterior surface of the patella through half its thickness

this fills rapidly with a delicate highly vascular granulation tissue from the marrow spaces which in this portion of the bone are numerous. Osteal fibroblasts from the marrow spaces grow out along the capillaries and deposit new bone, the trabeculæ of which extend in lines parallel to the long axis of the hole. At the posterior surface of the hole where pressure is exerted on the medullary procallus granulation cartilage is formed.

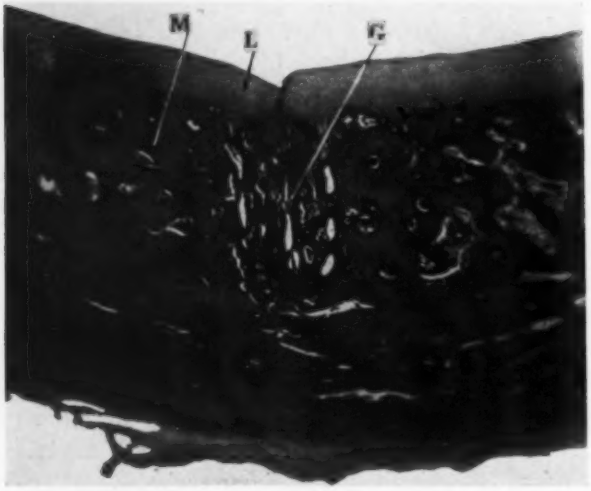


FIG. 19.—Drill hole through posterior surface of patella of dog showing: G—Hole filled with new bone, the trabeculæ of which lie in lines of pressure. L—New cartilage which has buckled because of the bending of the weakened patella through tension. M—Original trabeculæ of patella which lie for the most part in lines of tension.

That this new cartilage is not formed by proliferation of the surrounding preëxisting articular cartilage was demonstrated by a series of three experiments performed by Dr. Leonard W. Ely and the writer, to determine the effect of injury to the joint tissues of rabbits and to study the processes of repair in them and especially to observe the reaction and repair of articular cartilage.

(1) An incision was made in the cartilage of the patella and in the cartilage of the intercondylar groove of the femur.

(2) The cartilage over the same areas was scraped off without injury to the underlying bone buttress.

(3) The cartilage and underlying bone buttress were removed.

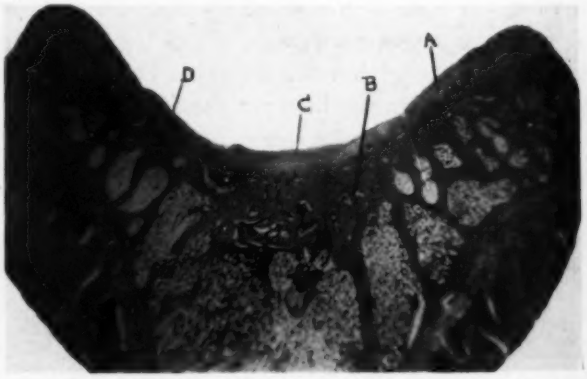


FIG. 20.—Intercondylar groove of femur of rabbit, showing: A—Original articular cartilage. B—New bone buttress at site of removal of articular cartilage and underlying bone buttress. C—New cartilage developed from medullary procallus granulations through pressure and motion of overlying patella. D—Absence of cartilage in area in which articular cartilage was removed without injury to underlying bone buttress.

Following incision or removal of the articular cartilage without removal of the underlying bone buttress, there was no repair of cartilage. When however, the underlying bone buttress was removed with the cartilage, thus opening up the marrow spaces, the marrow in the vicinity of the defect became fibrous in character. Procallus granulation tissue developing from

the vessels of the marrow invaded the clot filling the defect. Osteal fibroblasts proliferated along the capillaries and deposited osteoid material and bone. Where the procallus granulations were subjected to pressure and motion fibrocartilage was formed which is easily differentiated from the original articular cartilage.

If ununited fracture is the result of local anatomical conditions such as (1) absence of subperiosteal callus, (2) the prevention of fusion of the internal or medullary procallus granulations of the fragments by the ingrowth of dense, relatively avascular fibrous tissue from the lacerated periosteum, and (3) the closure of the marrow spaces of the ends of the fragments by an osseous plug or bony buttress, we ought to be able to secure bony union by converting a case of non-union into a simple fracture, without the introduction of osteogenetic elements from without, as, for example, by the use of an autogenous bone graft. In order to convert this type of non-union into a simple fracture, it is necessary (1) to elevate the periosteum for a short distance on either side of the fibrous bond, (2) to remove the fibrous band, (3) to open up the medullary spaces of the ends of the fragments, and (4) to prevent the recurrence of fibrous tissue ingrowth between the fragments.

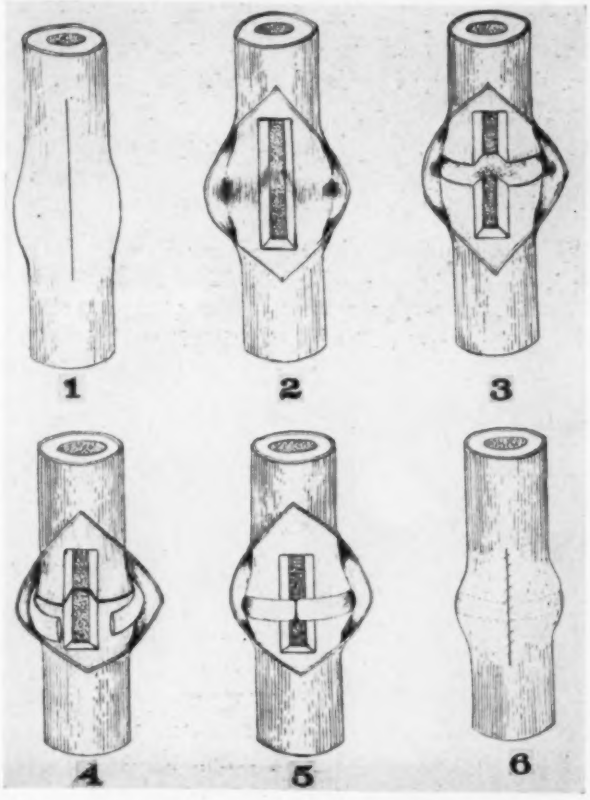


FIG. 21.—Schema to illustrate steps in operation for ununited fracture. 1—Incision of periosteum. 2—Lifting up of periosteum and thin flake of cortical bone and trough in fragments. 3—Removal of fibrous bond. 4—Approximation of fragments, with (5) fragments held in place with thin band of cortex of rib. 6—Suture of the periosteum.

With a tourniquet applied to the part an incision is made through the periosteum extending from one fragment to the other across the fibrous bond. Histologic examination of our experimentally produced specimens of non-union showed that in the healing process the fibrous layer of the periosteum becomes continuous over the fibrous bond. The periosteum and a thin shell of cortical bone is lifted up for a short distance on either side of the bond and separated from the latter. By lifting up a thin portion of

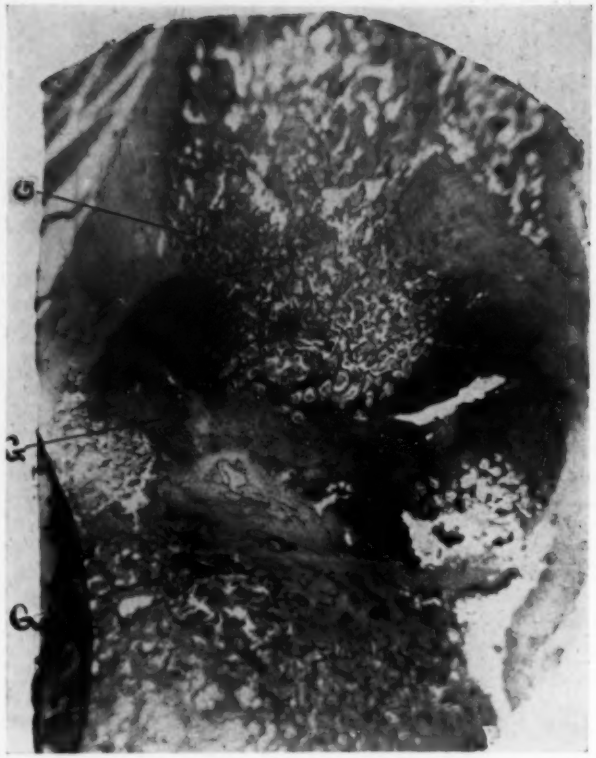


FIG. 22.—Fracture of ulna experimentally produced on the dog. In this experiment the periosteum was incised and fracture produced with a fine saw. The periosteum was then lifted up for a short distance on either side of the fracture line and a piece of egg membrane inserted about the fracture line between the periosteum and the cortical bone. Note—D, absence of fibrous tissue, the bones are united by the internal or medullary calluses, the vessels of which have fused. New bone, G, is being deposited about the vessels.

FIG. 23.—End result following operation for experimentally produced ununited fracture of tibia of dog. No bone graft was used. R—Area of union, showing increase in thickness of cortex; some medullary osseous callus still remains.

FIG. 24.—Ununited fracture of ulna in human showing: I—Area of non-union. Note osseous plug in upper end of lower fragment. G—Area of operation without bone graft to show increase in diameter of bone at site of lifting up of periosteum.

the cortical bone with the periosteum the continuity of the latter is less apt to be interrupted.

The fibrous bond is removed and a trough is made with a circular saw and chisel, in a manner similar to the trough for an inlay graft. At the union of the fibrous bond and periosteum the latter is ragged and to prevent proliferation and ingrowth of fibrous tissue and at the same time secure fixation of the fragments, a thin piece of the cortex of a rib is rolled up into a band and inserted about the ends of the fragments at the line of separation. The periosteum is now closed and the wound in the soft parts sutured. A dressing is applied and the tourniquet removed.

FIG. 25.—Final result of operation for ununited fracture of tibia without bone graft or internal fixation with rib showing increased diameter of bone at area of elevation of periosteum. Note small area of decreased density on mesial aspect of tibia where fibrous tissue of the periosteum has grown in between the fragments.

Blood fills the space between the periosteum and cortical bone, the trough in the fragments and the space between the ends of the fragments. Procallus granulations from the open haversian canals and marrow spaces develop, invade, and replace the clot. The granulations fuse and thus reëstablish vascular communication between the fragments. Osteal fibroblasts proliferate along the capillaries and new bone is deposited, forming well-defined subperiosteal and medullary calluses which unite the fragments by osseous union.

The internal fixation of the fragments by means of a thin band of cortex of a rib might be considered as the introduction of osteogenetic elements from without. In order to demonstrate that this procedure is not necessary to secure bony union, we substituted a piece of egg membrane for the cortex of rib and secured bony union. After removal of the fibrous bond and after opening up the marrow spaces in a case of experimentally produced non-union in the fibula of a dog, a strip of egg membrane obtained by boiling an egg for five minutes and dropping it into cold sterile water, was placed about the ends of the fragments, beneath the periosteum in a manner similar to the application of an internal fixation band. Blood filled the trough and the space between the fragments. Procallus granulation masses of the fragments fused and osteoid material and bone united the fragments in a short time.

egg membrane inserted about the fracture line of fibrous tissue, osteum and the cortical bone. Note—D, absence of fibrous tissue, the bones are united by the internal or medullary calluses, the vessels of which have fused. New bone, G, is being deposited about the vessels.

ous callus still remains.

In our later cases of non-union in the human no means of internal fixation or means of preventing ingrowth of fibrous tissue has been used and bony union has occurred.

In these cases, therefore, no osteogenetic tissue has been added from without nor has there been any alteration in the blood supply, nerve supply, calcium metabolism or other conditions, to which non-union has been attributed.

CONCLUSIONS

Our röntgenologic, microscopic and experimental studies of non-union point to local anatomical conditions as the cause of non-union. These anatomical conditions are the result of laceration of the periosteum usually flush with the fracture line and separation of the fragments. As the periosteum remains adherent or in close contact with the cortical bone little or no subperiosteal callus develops.

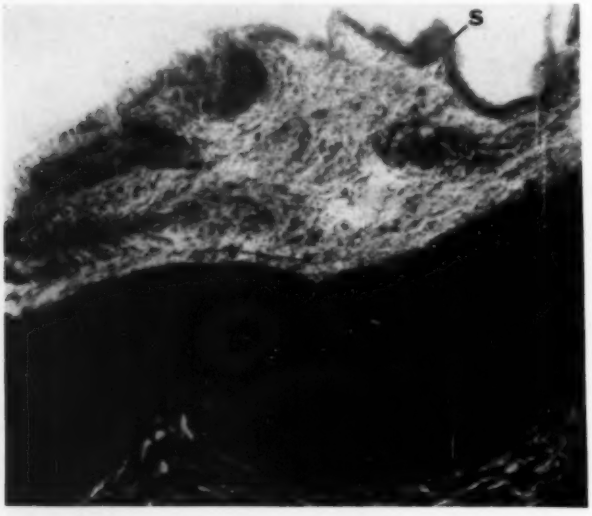


FIG. 26.—S—Tissue resembling synovial membrane from pseudarthrosis experimentally produced in dog. This tissue is found in portions of joint where there is motion without pressure.

Union is therefore dependent upon the less active and less abundant medullary procallus granulation masses, which are prevented from fusing and from reëstablishing vascular communication between the fragments by the ingrowth of the dense avascular fibrous tissue from the periosteum. This latter acts as a limiting membrane.

With slight separation and immobilization of the fragments, firm fibrous union occurs, the fibres of the bond running for the most part parallel to the ends of the fragments. With moderate separation of the fragments and tension on the granulation tissue due to gravity, or muscular contraction, loose fibrous union results. The bond is similar in structure to a tendon, and the fibres of the bond extend in the direction of tension, for the most part parallel to the long axes of the fragments. The contour of the bone ends will depend upon the relative rates of growth of the subperiosteal and medullary procallus granulations and of the ossification of the latter. If the medullary procallus granulations have completely ossified the ends of the fragments will be serrated and irregular.

If after the development of fibrous union, restoration of function, particularly weight bearing occurs, the fibrous tissue is compressed. If, in addition to compression, there are sliding movements between the fragments, the

bundles of collagen fibres are ground and torn and irregular slits or clefts with ragged walls appear. Continued compression with motion causes necrosis of these fibres and they are gradually absorbed or remain in the clefts or joint space as débris. If ossification of the medullary procallus is incomplete at the time when motion and pressure begin, the ends of the fragments become rounded off, smooth and capped with fibrocartilage.

The end of the upper fragment is usually convex, while that of the lower fragment is concave. In those portions of the pseudarthrosis where motion is present but pressure absent a tissue resembling synovial membrane is seen.

The present investigation has been conducted with the hope of adding to our knowledge of the cause of non-union following fracture of the long bones. No attempt has been made to devise a new method of surgical treatment of non-union. The methods of the massive graft and bone chips have their indications and have been successful in the experience of many surgeons. The operative procedure described above has been used successfully in cases of non-union experimentally produced in the dog, and in cases of non-union in the human, in which there were good alignment and slight separation of the fragments. The procedure demonstrates that bony union can be secured unaided by the introduction of osteogenetic elements from without, by converting these cases of fibrous union into simple fractures and preventing the ingrowth of fibrous tissue from the lacerated periosteum.

THE EDUCATIONAL VALUE OF THE FOLLOW-UP

A REPORT OF 14 YEARS—FROM THE FIRST SURGICAL DIVISION (CORNELL MEDICAL) OF THE NEW YORK HOSPITAL

By Charles L. Gibson, M.D.

of New York, N. Y.

In the Annals of Surgery, December, 1919, a report of our Follow-Up work for a period of six years, ending January 1, 1919, was given. There was then described briefly an outline of the methods employed. We have made no radical change subsequently. Appended to this present report is a review of our follow-up work, continuing the first series and bringing it up to January 1, 1927, a total period of fourteen years.

It would seem wisest not to attempt to publish the combined figures of these two periods, as the character of the work at present naturally has undergone considerable deviations from the original period and the combined statistics would not necessarily show the usefulness of the present-day methods. Attention, however, will be called to a selected group of cases, contrasting results obtained in the two periods.

The lessons taught have been very striking and we have found that in some instances we have greatly improved our results by taking to heart the bad results and analyzing their causes and seeking to remedy the deficiencies.

There have been several partial reports on follow-up; notably two series of cases of chronic appendicitis; the first published in the *American Journal of the Medical Sciences*, May, 1920, the second in the *American Journal of the Medical Sciences*, December, 1924. In these we show some very poor results in the first group; but by applying the lessons learned we are able to show vastly better results in the second group.

A paper on the study of a twelve-year follow-up on "Final Results in the Surgery of Malignant Disease" was published in the Annals of Surgery, August, 1926, giving an accurate reflection of the very disheartening results of the treatment of malignant diseases in such material as we have.

The following statement summarizes the situation. "Of the 437 operative cases who came under our observation, only sixty-four are living to-day with-

Table I.

Comparison of Two Periods.

	1913–1919	1919–1927
Number of cases	8,456	12,144
Number of operations	7,175	9,025
Operative mortality	4 %	4.6%
Per cent. of cases having follow-up report	75.5%	95.9%
Unsatisfactory results	13.3%	6.9%

out recurrence and only thirteen have survived the artificial and questionable time limit of five years."

All these follow-up systems are based on ward patients alone, as we have felt that we could not exercise the same rigid scrutiny of these private patients as is desirable, and it did not seem wise to have any double standard.

It will be noted the increasing effectiveness of the follow-up system, 96 per cent. of patients have been observed in the second period as opposed to 75 per cent. in the first.

The unsatisfactory results in the second period have been almost halved.

A disquieting increase in the mortality in the second period, 4.6 per cent. as opposed to 4 per cent., has attracted our attention. One explanation may be the increasing number of important cases and more radical surgery, especially in malignant diseases; also, the increasing mortality in appendicitis which we have noted as have other clinics throughout the world.

The term "unsatisfactory" means that we have not accomplished the results generally sought for in operative treatment. In the case of malignant disease this might represent either an extension of the process or failure to relieve it entirely, as for instance palliative operation or recurrence of the condition. In the case of herniæ it will mean naturally a recurrence of the hernia.

TABLE II.

Digestive System.

	1913–1919	1919–1927
Acute appendicitis	782 operations 34 deaths (4.3%)	990 operations 58 deaths (5.7%).
Chronic appendicitis	552 operations 30% unsatisfactory	773 operations 7% unsatisfactory.
Cholecystitis and cholelithiasis	179 operations 12 deaths (6.7%)	347 operations 41 deaths (11.8%).
Tonsils	559 operations 1 death (epidemic meningitis)	1086 operations No deaths.
Ulcer of stomach and duodenum	70 operations 6 deaths (8.5%) 9% unsatisfactory	169 operations 16 deaths (9%) 2% unsatisfactory.
Ulcer of stomach and duodenum, perforating, acute	39 operations 10 deaths (25.6%)	63 operations 11 deaths (17.4%).
Abscess of liver	100% mortality	100% mortality.
Adhesions of peritoneum	29% unsatisfactory	22% unsatisfactory.
Hemorrhoids	184 operations 0 deaths 3 unsatisfactory	168 operations 0 deaths 2 unsatisfactory.
Intestinal obstruction	36 operations 15 deaths (41.6%)	39 operations 18 deaths (46%).

This report will take up the question both of unsatisfactory results and the general mortality of groups.

Acute Appendicitis.—An increase from 4.3 per cent. to 5.7 per cent. mortality is in accordance with the findings quoted above. It is most interesting to note that patients coming under treatment early—our standard is whether or not the wound can be closed without drainage—the mortality is that of an interval appendicitis, as only one in two hundred dies, and these deaths occur largely in the more advanced period of life and are due to incidental complications such as pulmonary embolism.

In drained cases the mortality with no involvement of peritoneum is 2.10 per cent.; with localized abscess 3.26 per cent.; and with a definite peritonitis with no limiting adhesions 20.92 per cent.

Attention is also called to the rarity of fecal fistulæ by our methods of drainage, and their very benign character, usually closing up spontaneously without operative procedure. "Prophylaxis of Fecal Fistula in Operations for Acute Appendicitis," *American Journal of Surgery*, January, 1926.

Patients who have been operated on for acute appendicitis are generally greatly improved in health and their return complaints are practically negligible. With wide open drainage—use of the Mikulicz tampon, naturally a certain proportion of herniæ is to be expected (14 per cent.). We always recommend young and vigorous individuals to have these herniæ repaired, as these operations are very easy as there is no loss of tissue, particularly fascia, the wide open drainage doing away with secondary sloughing of the tissues of the abdominal wall.

Cholecystitis and Cholelithiasis.—The increase in the mortality percentage is rather discouraging. On the other hand, the second series represents a greater proportion of more extensive operations and the gradual tendency to discard the simple drainage operations. In the last two years the method of operating has become better standardized and made easier, by the safer employment of subperitoneal excision. "Aids to Cholecystectomy," ANNALS OF SURGERY, May, 1926. The more recent results have shown distinct improvement.

Ulcer of Stomach and Duodenum.—The mortality remains the same; but the second series shows a very much larger proportion of radical operations. For all practical purposes no other treatment, but resection, for gastric ulcer is performed to-day. The greatly reduced percentage of unsatisfactory results, 2 per cent. as opposed to 9 per cent., is an eloquent argument for the value of more radical surgery.

Perforating Ulcers of Stomach and Duodenum.—In the treatment of perforating ulcer of the stomach and duodenum, it is our policy to deal only with the actual condition, such operations as gastro-enterostomy, exsection of the ulcer, resection of the pylorus being performed only when the indications are those of absolute necessity.

Few classes of cases make a better comeback than the patient with an acute

perforation. Eighteen per cent. have some trouble, either post-operative adhesions or stenosis of the pylorus requiring a secondary operation.

Abscess of Liver.—Attention is called to the 100 per cent. mortality in abscess of the liver. We have no proper explanation for this fact.

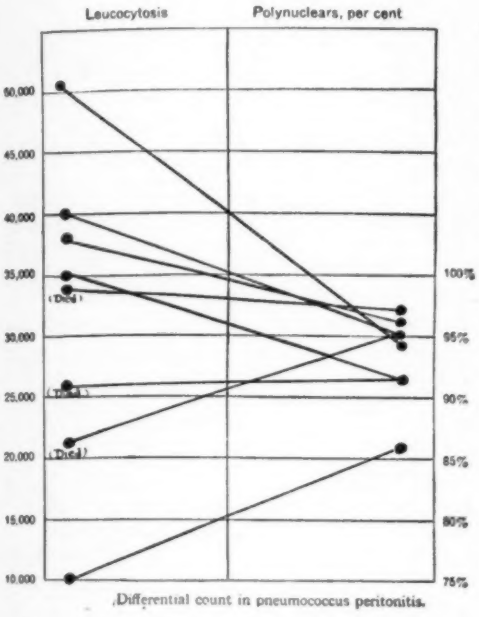


FIG. 1.—From "Pneumococcus Peritonitis," *Transactions of the American Surgical Association*, 1925.

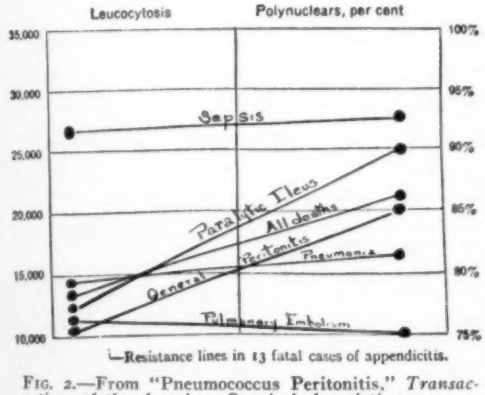


FIG. 2.—From "Pneumococcus Peritonitis," *Transactions of the American Surgical Association*, 1925.

Intestinal Obstruction.—The mortality of the two periods is respectively 41.6 per cent. and 46 per cent. Intestinal obstruction is still the most unsatisfactory form of acute abdomen. Although refinements of diagnosis, increase in the number of skilled and experienced operators, and better facilities now exist, the mortality of intestinal obstruction remains about the same as when I first started to do surgery and I think that this state of affairs exists universally.

It is entirely a question of early diagnosis and prompt relief. The general practitioner seems to get no idea of what intestinal obstruction is until the patient shows the "classical" symptoms, which means he is very nearly moribund and in addition will require, perhaps, a severer operation for relief as opposed to a very simple one—division of band, reduction of a volvulus and intussusception in the early stages.

There is no phase of surgery which calls for missionary work more than the education of the practitioner. He should be instructed that a mistaken diagnosis of possible early obstruction will generally result in a patient's surviving and chances can be taken accordingly.

Pneumococcus Peritonitis.—This seems to be diminishing in frequency as our diagnostic ability and resources seem to be on the increase.

The behavior of the blood count in pneumococcus peritonitis is so typical that our attention is at once called to the possibility. There is a very high percentage (Fig. 1) of total leucocytosis with a high percentage of polymor-

phonuclears; a contrast to the spreading peritonitis of appendicitis (Fig. 2) where the total leucocytosis as plotted out on my standard chart, is on a much lower level on the whole than the percentage of polymorphonuclears.

TABLE III.

Thyroid.

	1913–1919	1919–1927
Goitre—simple and hyperthyroidism	9 operations 0 deaths Follow-up result 100% satisfactory	48 operations 5 deaths Follow-up result 100% satisfactory.
	Note:—In the first series of cases 8 were asked to return for examination; but only 4 returned. 100% is based on these four cases who came back and had satisfactory results. In the second series 43 cases were asked to return and 43 cases returned. 100% is based on 43 cases instead of 4.	
Goitre—exophthalmic	9 operations 2 deaths (22%) Follow-up, based on 5 cases who returned, 20% unsatisfactory	25 operations 5 deaths (20%) Follow-up, based on 20 cases who returned, 100% satisfactory.

Operations on the thyroid have given very gratifying after results and the proportion of permanent cures is very high. On the other hand, the mortality is much too high. The class of material coming to us is largely of the severer type and it is possible some of these patients should not have been operated on at all.

TABLE IV.

Herniæ.

	1913–1919	1919–1927
Femoral	53 operations 1 death No recurrences	40 operations No deaths No recurrences.
Femoral, strangulated	11 operations 1 death (9%) No recurrences	23 operations 1 death (4%) No recurrences.
Inguinal	849 operations 2 deaths (.2%) 3.7% recurred	895 operations 4 deaths (.4%) 3.1% recurred.
Inguinal, strangulated	41 operations 6 deaths (14%) 2 recurrences	58 operations 4 deaths (7%) 2 recurrences.
Umbilical	21 operations 2 deaths (9%) 1 recurrence	31 operations 1 death (3%) 2 recurrences.

Umbilical, strangulated	9 operations 5 deaths (55%) 1 recurrence	11 operations 2 deaths (18%) 2 recurrences.
Ventral	39 operations 2 deaths (5%) 1 recurrence	89 operations 2 deaths (2%) 9 recurrences.
Ventral, strangulated	5 operations 3 deaths (60%)	7 operations 2 deaths (28%).

On the whole, our herniæ results are satisfactory. We have not resorted to any unusual and, I think, generally unnecessary procedures such as the Gallie operation, relying on doing the conventional and perfectly satisfactory operations in a thorough and radical manner, *e.g.*, using great care to isolate and remove direct sacs and transplanting the rectus muscle and fascia for the plastic repair of the canal.

The more extensive use of local anæsthesia in the various types of strangulated herniæ, especially umbilical and ventral, has greatly reduced the mortality.

We continue to use for the extreme incisional hernia the operation described in the ANNALS OF SURGERY for August, 1920, with increasing satisfaction, and believe it is the solution of this problem as we have not refused any case that came to us, no matter how extensive, and have had only one partial recurrence in this whole series.

We are applying this same principle more and more to the ordinary umbilical hernia, believing it is more efficacious than the overlapping Mayo-Blake operation.

TABLE V.

Reproductive Organs.

Female.

	1913–1919	1919–1927
Extrauterine	51 operations 2 deaths (4%) Unsatisfactory 12%	52 operations 4 deaths (7.6%) Unsatisfactory—0.
Chronic salpingitis	211 operations 5 deaths (2%) Unsatisfactory 10%	164 operations 5 deaths (3%) Unsatisfactory 12%.
Prolapse of uterus	21 operations 1 death (4.7%) Unsatisfactory 20%	23 operations 0 deaths Unsatisfactory 9%.

Male.

Hydrocele	62 operations 0 deaths Unsatisfactory 3%	68 operations 0 deaths 0 unsatisfactory.
Varicocele	78 operations 0 deaths Unsatisfactory 2.7%	31 operations 0 deaths Unsatisfactory 3.7%.

Prolapse of Uterus.—The second period shows considerable diminution in the per cent. of unsatisfactory operations, the result from taking to heart the large percentage of unsatisfactory in the first period. The tendency has been to do more radical operations and these have been applied in increasing frequency to the severest cases.

A very satisfactory operation for the bad cases is a thorough repair of the rectocele and cystocele and then a suspension of the uterus, either by a very taut plication of the ligaments or performing a supravaginal hysterectomy and reimplanting the ligaments in the stump of the cervix and bringing the bladder on top and back of the uterine stump.

TABLE VI.

Respiratory System.

	1913–1919	1919–1927
Suppurative pleurisy	84 operations	134 operations
	13 deaths (14.6%)	13 deaths (9.6%).
	Reoperations 7.8%	Reoperations 8%.
	Unsatisfactory 4.4%	Unsatisfactory 3.3%.

There is a marked drop in the mortality of empyema.

The experience gained from the treatment of empyema during the War has been applied to good advantage, in the realization of the great difference between the influenza empyema and the ordinary pneumococcus empyema, and the difference in character of treatment.

Massive Collapse.—Of late we have detected massive collapse of the lung, with increasing frequency and have been relieved to recognize the underlying condition which always gets well, quieting our fears of a possible impending pneumonia. Since this report was closed we have had two extraordinary examples of the cause of massive collapse and its cure.

Our present House Surgeon, Dr. Wade Duley, conceived the idea of placing the patient on the sound side and hitting the chest a smart slap on the affected side causing the patient to make violent expulsive efforts and bring up a large plug of muco-pus. The clinical symptoms were relieved at once and X-ray pictures taken respectively a half hour and fifteen minutes after showed almost complete reaëration of the chest, with a return of the heart and trachea to their normal position.

TABLE VII.

Pulmonary Embolism—1919–1927.

No. of cases following operation—35
Of these 11 lived.
24 died.
No. of cases without operation—2
Both died.
No. of operations performed in this period—9025
24 or .3% died of pulmonary embolism.
Out of 990 operations for acute appendicitis 2 (.2%) died of pulmonary embolism.
Out of 773 operations for chronic appendicitis 2 (.2 plus %) died of pulmonary embolism.

Out of 1,171 operations for hernia, 7 cases (.5%) died of pulmonary embolism.
Out of 347 operations for gall-bladder disease 2 (.5%) died of pulmonary embolism.
Out of 600 operations on the pelvic viscera 2 (.3%) died of pulmonary embolism.
Out of 763 operations on remaining gastro-intestinal conditions 4 (.5%) died of pulmonary embolism.

TABLE VIII.

Fractures.

	1913–1919	1919–1927
Fractures	236 cases returned	724 cases returned.
	53 excellent	314 excellent.
	162 satisfactory	395 satisfactory.
	21 unsatisfactory 8.8%	15 unsatisfactory 2%.

Following the impetus of the War, in accordance with the general tendency to give more special attention to fractures, the gratifying reduction to 2 per cent. unsatisfactory cases is noted.

The mortality of gunshot wounds of the abdomen continues to be very high (60 per cent. for entire period). A number of these of course are multiple injuries, including the thorax. Here again, contrary to many optimistic statements, modern surgery has not brought any signal relief.

TABLE IX.

Fracture of Skull.

	1913–1919	1919–1927
No. of cases	43	66
Operations	10*	5†
Died following operation	6	0
Died without operation	8	25
Total mortality	32.5%	37.8%
Operative mortality	60 %	0
% operative cases	23.2%	7.5%

* Nine for decompression; one suture of laceration.
† Four for decompression; one for removal of bullet and mastoidectomy.

The mortality of fracture of the skull does not change very much and keeping it under 40 per cent. is on the whole quite good.

It has not been our policy to resort so freely to operation as has been recommended by so many surgeons as we believe there is very little indication except for the relief of pressure, whether by epidural clot or bone.

A very good paper by McCreery and Berry, read before the New York Surgical Society, April 20, "A Study of 520 Cases of Fractures of the Skull" from material from the First Surgical Division of Bellevue Hospital, gives a total mortality of 39 per cent. and an operative mortality of 53 per cent.

In both Bellevue Hospital and the New York Hospital the material is brought in by the ambulance and covers very much the same sort of district.

The Use of Insulin.—The second period has also witnessed the introduction of insulin † which has been a valuable adjunct for the preparation of

† "The Mortality of Surgical Complications in Diabetes", W. Morris Weeden, Journal of A. M. A., April 12, 1924.

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Congenital Abnormalities and Malformations.						
Branchial cyst	2		2	2		
Tongue	2		2		2	
Intestines	3	3	3			
Stomach	1		0			
Mesenteric artery	1		1	1		
Bones	2		0			
Thyroglossal cyst	7		6	6		
Ears	1		1		1	
Lip and palate	13	3 (1)	12	3	3	1
Feet	4		3	2	2	
Hands	3		3	2	1	
Muscles	1		1		1	
Ribs	4		3		2	1
Uterus	2		2	1	1	
Vagina	2		1	1		
Penis	3		1		1	
Testicle	12		11	7	3	
Bladder	2	1	2	1		
Kidney	4		2		2	
Blood.						
Leuchæmia	2		0		1	
Splenic anemia	7	2	6		3	
Hemorrhagic pupera	2	1	2	1		
Secondary anemia	1		0			
Hemophilia	2		0		1	
Pernicious anemia	4	1	4		2	
Diseases of Bones.						
Chondrodystrophia fœtalis	1		0			
Curvature of spine	3		0			
Deformity of mandible, acquired	1		0			
Epiphysitis	1		0	1		
Faulty union	26		25	2	19	3
Necrosis	1		1	1		
Osteomyelitis	159	11	155	48	79	9
Osteomalacia	1	1	1			
Periostitis	8		6	3	2	
Bursæ.						
Bursitis	37		34	20	14	
Circulatory Systems.						
Aneurism	8	1	6	2	2	
Arteriosclerosis	2		1		1	
Endarteritis obliterans	16		11	1	9	
Phlebitis	2		0			
Varicose veins	55	1	51	26	18	2
Cardiac valvular disease	2		0			
Myocarditis	1	(1)	0			
Ac. purulent pericarditis	1	1	1			

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
			Digestive System.			
Appendicitis, acute	998	58	990	697	182	10
Appendicitis, chronic	820	7	773	460	218	52
Cholecystitis and cholelithiasis	423	41	347	186	97	12
Adhesions about gall-bladder	2		1	1		
Cholangeitis	2	1	2		1	
Stenosis of gall-bladder	1		1		1	
Biliary fistula	1		1		1	
Abscess of intestine	1	1	1			
Colitis	10		4	1	2	
Constipation	29		0			
Cyst of mesentery	1	1	1			
Diverticulitis	6		6	3	3	
Duodenitis	1	1	1			
Enteritis (acute)	1	(1)	0			
Fecal fistula	2		2	1	1	
Gastro-enteritis	5		0			
Intestinal hemorrhage	1		1	1		
Mesenteric thrombosis	3	3	3			
Intestinal neurosis	3	1	1			
Intestinal obstruction	43	18	39	8	7	5
Splanchnoptosis	16		0			
Ulcer intestine	4	2	4	2		
Abscess of liver	7	6	7			
Cirrhosis	4	2 (1)	2			
Hepatitis	1	1	1			
Deformity of palate acquired	1		1	1		
Angina ludovici	1	1	1			
Stomatitis	1		0			
Abscess pharynx	9		9			
Pharyngeal hemorrhage	1		0			
Chr. inflammation of salivary gland	1		1	1		
Acute parotitis	2	1	2		1	
Fistula of salivary gland	1		1	1		
Tonsils & Adenoids	2025		1086			
Tonsillar abscess	17		13			
Acute glossitis	1		0			
Foreign body in œsophagus	1		0			
Torsion of omentum	2		2	2		
Pancreatitis	10	2 (1)	7	2	4	1
Adhesions of peritoneum	120	5	78	24	32	16
Pelvic abscess	14	2	12	4	4	
Subphrenic abscess	1		1	1		
Peritonitis	16	11	16	3	1	
Peritonitis pneumococcus	5	3	5	2		
Abscess rectum	50	1	48	28	14	1
Fissure of anus	16		15	12	2	1
Fistula in ano	52		52	30	13	2
Foreign body in rectum	1		1	1		
Hemorrhoids	179		168	124	23	2
Proctitis	3		0			
Prolapse rectum	8		6	4	1	1
Pruritis	2		1			1
Spasm of rectum	1		1	1		
Stricture of rectum	2		2	1	1	
Ulcer of anus	1		1			
Achylia gastrica	1		0			
Adhesions about stomach	1		0			
Cardiospasm	1	1	1			

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Digestive System—(Continued)						
Nervous dyspepsia	3		0			
Gastroduodenitis	2		0			
Gastritis	9		1	1		
Gastroptosis	6		0			
Hypochlorhydria	1		0			
Hematemesis	2	1	1		1	
Pylorospasm	3		0			
Ulcer stomach	64	13	51	20	15	
Ulcer duodenum	132	3	118	73	36	4
Ulcer stomach, ac. perf.	30	4	29	9	15	
Ulcer duodenum, ac. perf.	35	5	34	12	16	
Ulcer stomach, chr. perf.	3	1 (1)	2		1	
Ulcer duodenum, chr. perf.	4		4	2	2	
Pyloric stenosis	2		2	1	1	
Ductless Glands and Spleen.						
Goitre, simple	49	5	48	37	6	
Goitre, exophthalmic	25	5	25	14	6	
Hemorrhage into subrenal gland	1	1	1			
Ear.						
Mastoiditis	8		8	6	1	1
Otitis media	2		0			
Herniæ.						
Epigastric	18		16	9	5	1
Femoral	41		40	28	10	
Femoral, strang.	23	1	23	12	7	2
Inguinal:						
Indir., l. side	652	2	617	509	66	9
Direct, l. side	78		75	61	6	6
Dir. and indir., l. side	81		80	68	5	5
Bilat. indir.	74	2	65	52	6	3
Bilat. dir.	15		15	12	2	1
Bilat. dir. and indir.	43		43	35	4	3
Inguinal, strang.	63	4	58	48	4	2
Diaphragmatic hernia	1		0			
Internal hernia, strang.	1		1	1		
Umbilical	35	1	31	23	3	2
Umbilical, strang.	11	2	11	4	2	2
Ventral	98	2	89	52	18	9
Ventral, strang.	7	2	7	3	2	
Infective Diseases.						
Abscess	142	1 (1)	136	72	21	4
Carbuncle	37	3	37	15	6	2
Cellulitis	309	7	285	118	114	22
Chicken pox	1		0			
Diphtheria	4		0			

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Infective Diseases—(Continued).						
Erysipelas	1		0			
Fever—unknown origin	1		1		1	
Furunculosis	2		2	1		
Gonococcus infection	12		4	2	1	
Rheumatic fever	2		0			
Syphilis	31		5		2	
Tuberculosis of:						
Bones	22	2	15	3	9	
Digestive system	24	3	19	1	6	4
Joints	20		12	4	5	1
Lymph-nodes	82		76	9	54	8
Muscular system	2		2		1	1
Reproductive organs—female	11	2	11	2	5	
Reproductive organs—male	12		9	2	2	1
Respiratory	6		1			
Skin	2		1			1
Urinary	21	1	9	3	5	
Ac. miliary	3	3	3			
Typhoid fever	1		1	1		
Joints.						
Ankylosis	17		13		11	1
Arthritis	65		46	8	34	2
Arthritis deformans	1		0			
Contracture of joint	5		5		5	
Coxa vara	1		1		1	
Genu varum	3		1		1	
Genu valgum	3		3	1	2	
Hallux valgus	12		9	3	6	
Pes planus	3		3	1	2	
Pes valgus	2		2		2	
Talipes	3		3		2	
Trigger thumb	1		1			1
Loose body in joint	1		1		1	
Lymphatic System.						
Abscess	27		27	20	4	
Lymphangitis	5		0			
Lymphadenitis	40		34	21	7	
Elephantiasis	3		2		1	1
Hodgkin's disease	9		2			3
Diseases of the Mind.						
Psychosis	3		0			
Miscellaneous.						
Acidosis	2		0			
Amputation stump	10		8	4	4	
Cicatricial contracture	21		21	3	15	2

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Miscellaneous—(*Continued*).						
Diabetes	2		0			
Gangrene—diabetic	10	5	9	1	2	
Gangrene—arteriosclerotic	3	2	3		1	
Gangrene—traumatic	1		1		1	
Gout, acute	1		1			1
Hypertrophic osteo-arthropathy	2		0			
Malingering	1		0			
Migraine	1		0			
Obesity	1		0			
Rickets	5		0			
Scurvy	1		0			
Shock	1		0			
Shell shock	1		0			
Sinus, P.O.	13		11	4	6	
Unknown	26		3	1	2	
Muscular System.						
Abscess	2		2	2		
Contracture of muscle	8		8	1	3	4
Contracture of tendon	3		3		2	1
Ganglion	7		6	6		
Hammer toe	6		6	5		
Myositis	5		3		2	
Tenosynovitis	15		14	4	6	4
Nervous System.						
Abscess of brain	2	(1)	1	1		
Epilepsy	4	1	2		1	
Hemorrhage into cerebrum	1	(1)	0			
Hysteria	4		0			
Meningitis—cerebrospinal	1	1	1			
Neuralgia	5		0			
Neurasthenia	4		0			
Neurolysis	2		2		2	
Neuritis	2		0			
Post. poliomyelitis	12		11	1	9	1
Paralysis	4		1			
Neurosis	1		0			
Tabes dorsalis	2		0			
Tic	1		0			
Thrombosis of sigmoid sinus	1		1	1		
Parasites.						
Actinomycosis	2	1	2		1	
Echinococcus	6	2	6	2	1	
Dysentery entamoebic	1		1	1		
Oxyuris vermicularis of appendix	1		1	1		
Poisonings.						
Chlorine	5		0			
Lead	1		0			
Sulphuric acid	1	1	1			

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Reproductive Organs (Female).						
Functional disturbances	25		9	3	3	1
Abscess breast	28		27	23	3	1
Mastitis	24		19	17	1	
Abscess ovary	3		2		2	
Extrauterine	56	4 (1)	52	37	14	
Hematosalpinx	3		3	2	1	
Hydrocele of round ligament	1		1	1		
Oophoritis	1		0			
Salpingitis, acute	70	2	46	25	13	
Salpingitis, chr.	180	5	164	79	51	16
Anteflexion uterus	8		8	2	4	2
Prolapse uterus	24		23	12	8	2
Retroversion uterus	46		39	17	15	5
Retroflexion uterus	2		2		1	1
Endocervicitis	1		1	1		
Endometritis	102	3	100	40	32	12
Endotrachelitis	1		1		1	
Hypertrophy of cervix	1		0			
Hypertrophy of round ligament	1		1		1	
Laceration cervix	7		6	3	3	
Metritis	4	2	4	2		
Stricture of uterine canal	1		1			1
Subinvolution of uterus	3		2		2	
Vulvo-vaginal abscess	4		4	2		
Abscess of Bartholin's gland	9		9	6	3	
Adhesions about clitoris	1		1	1		
Atresia of vagina	2		2			
Hyp. of vulva	1		1		1	
Lac. pelvic floor	62		60	29	27	3
Relaxed pelvic floor	65		60	22	28	7
Vulvitis	1		0			
Reproductive Organs (Male).						
Phimosis and redundant prepuce	125	(1)	116			
Abscess of prostate	2	1	2		1	
Chr. prostatis	1		1	1		
Enlargement of prostate	17	2 (1)	12	6	2	
Hematocele	3		2		2	
Hydrocele	75		68	57	7	
Varicocele	36		31	21	5	1
Epididymitis	5		2	1	1	
Respiratory System.						
Bronchitis	4		0			
Maxillary sinusitis	2		0			
Abscess of lung	8	6	8	1		
Pulmonary embolism	1	1	1			
Infarct of lung	1		1	1		
Supp. pleurisy	137	13 (1)	134	86	27	2
Pneumonia	6	(1)	2		1	
Ac. laryngitis	1	(1)	0			

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Skin, Hair and Nails.						
Cicatrix of skin	2		2	1	1	
Dermatitis	1		0			
Eczema	1		0			
Ingrowing toe nail and paronychia	10		10	5	4	
Keloid	1		1		1	
Leukokeratosis of cheek	1		1	1		
Ulcer of skin	23		9	2	6	1
Tumors (Benign).						
Adenoma of						
Breast	2		2	2		
Cervix	1	1	1			
Liver	1	1	1			
Rectum	1		1	1		
Uterus	1		1	1		
Angioma of						
Face	7		6	1	3	
Lower extremity	1		1	1		
Upper extremity	3		3	2		
Back	2		1	1		
Parotid	1		1		1	
Tongue	1		1			
Cystoma of						
Axilla	1		1		1	
Breast	1		1	1		
Broad ligament	1		1		1	
Buttock	2		2		2	
Cervix	1		1	1		
Eyelid	1		0			
Liver	1		1		1	
Neck	3		3	2	1	
Olecranon bursa	1		1	1		
Ovaries	100	2	89	50	29	3
Pancreas	1		1		1	
Scalp	3		3	1		
Ulna	1		1	1		
Fibroma of						
Breast	5		5	4	1	
Labium majus	1		1			
Mouth (epulis)	5		4	4		
Nose	1		1	1		
Ovary	1		1	1		
Rectum	1		1	1		
Jaw	1		1	1		
Lipoma of						
Chest wall	1		1	1		
Neck	8		7	7		
Back	9		9	8	1	
Scalp	1		1	1		
Upper extremity	15		15	8	4	
Lower extremity	8		8	4	1	1
Myeloma, multiple	1		0			
Neuroma of						
Arm	2		1	1		
Sublingual	1		1		1	

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Tumors (Benign)—(Continued).						
Osteoma of						
Femur	2		2	2		
Os Calcis	2		2	1	1	
Tibia	2		2		1	
Papilloma of						
Face and mouth	5		5	4		
Finger	2		2	2		
Cervix	4		4	1	3	
Urethra (caruncle)	5		4	3	1	
Vulva	1		1	1		
Perineum	1		1		1	
Descending colon	1		1	1		
Buttock	1		1			1
Rectum	7		6	4	1	
Uterus	1		1		1	
Retention cyst of						
Breast	1		1	1		
Broad ligament	1		1	1		
Face and neck	10		10	8	2	
Lingual duct	2		2	1	1	
Parotid	1		1	1		
Bartholin's gland	2		2	1		
Back	2		2	1		
Vaginal wall	1		1	1		
Scalp	1		1			
Upper extremity	4		4	3	1	
Lower extremity	1		1	1		
Rhinophyema	1		1	1		
Teratoma of						
Ovary	5	1	5	4		
Chest wall	2		2	2		
Sacrum (pilonidal cyst)	27		27	20	5	1
Unknown tumor of						
Ampulla vater	1		1		1	
Neck	1		0			
Spinal cord	1		0			
Mediastinum	1		0			
Thyroid	1		1			
Parotid	1		0			
Leg	1		0			
Adeno-angioma cervix	1		1	1		
Cystadenoma breast	3		3	3		
Cystadenoma ovary	2		2	1		
Fibroadenoma breast	8		8	7	1	
Fibrolipoma of skin						
of arm	1		1	1		
neck	1		1	1		
Fibromyoma uterus	138	6	125	75	41	2
Lymphangioma of						
Femoral canal	1		1	1		
Neck	1		1	1		
Neurofibroma of						
Thigh	1		1	1		
Osteochondroma of						
Tibia	1		1	1		
Ilium	1		1	1		

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Tumors (Malignant).						
Adenoma, malignant of sigmoid	1		1			
Carcinoma of						
Appendix	5		5	3		
Bone, frontal	1		1			
Breast	48	1	44		16	2
Bladder	3	1	1			
Gall-bladder	12	4	12			1
Intestines	37	21 (1)	36		5	
Kidney	2		1			
Larynx	3	(1)	1			
Lip	1		1			1
Liver	6	1	6			
Submaxillary gland	1		1		1	
Retroperitoneal lymph-nodes	1		0			
Mediastinum	1	(1)	0			
Mouth	1		0			
Œsophagus	7	1	3			
Pancreas	3	2 (1)	2			
Omentum	4	1	3			
Rectum	17	3	10		3	1
Penis	2		2		1	
Prostate	4		1			
Testicle	1		1			
Scalp	1		1		1	
Stomach	67	20 (1)	53		5	2
Tonsil	2		0			
Thyroid	2		1		1	
Ovaries	13	3	13		1	
Uterus	32	4 (1)	17		3	1
Epithelioma of						
Branchial cleft	1		0			
Face and scalp	9		7		2	1
Thumb	1		1			
Leg	2		1			
Lip	4		2			
Lymph-nodes	1		1			
Cervix	2		0			
Scrotum	1		1			
Shoulder	1		1			
Endothelioma of						
Chest wall	1		1		1	
Axillary nodes	1		1		1	
Hypernephroma of						
Kidney	2		2		1	
Melanoma						
Inguinal region	2		1			
Sarcoma of						
Bones	9	1	8		4	
Upper extremity	4		2		2	
Lower extremity	5		5			
Reproductive organs, female	4		3		2	
Back	1		1		1	
Kidney	3		1			
Maxilla	1		0			
Neck	3		3		2	1

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Tumors (Malignant)—(Continued.)						
Intestines	8	1	7			
Gum	1		1		1	
Lymph-nodes	7		4		2	
Retroperitoneal fascia	1		0			
Stomach	2		2		1	
Spleen	1	1	1			
Axilla	1		1			
Breast	1		1			
Myxochondroendothelioma	3		3		3	
Neurocytoma of Kidney	1		1			
Pancreas	1	1	1			
Teratoma of Testicle (malignant)	2		1			
Urinary Organs.						
Cystitis	11		0			
Calculus in bladder	2		1		1	
Retention of urine	2		0			
Perinephritic abscess	13		13	12	1	
Hydronephrosis	6	1	2	1		
Infarct of kidney	1		0			
Nephritis	4	(1)	2	1		1
Nephrolithiasis	41	1	19	8	5	3
Nephroptosis	8		2	2		
Pyelitis	35		2			
Pyelonephritis	1		1	1		
Pyonephrosis	9	1	4	1	2	
Ureteral colic	29		1		1	
Calculus in ureter	31		7	6	1	
Stricture ureter	7		1		1	
Stricture urethra	16	2	15	5	6	2
Urethritis	1		0			
Recto-urethral fistula	1		0			
Obstetrical Conditions.						
Abortion	77	(1)	65	25	15	
Accidental hemorrhage of pregnancy	1		1	1		
Mammillitis	1		0			
Pregnancy	12		0			
Septicæmia, Puerperal	1	(1)	0			
Toxemia of pregnancy	1		0			
Injuries.						
Fracture of Ankle-joint	43		3	18	24	
Clavicle	24		6	12	10	
Elbow	9		5	3	5	1
Bones of face	7		2	2	2	
Femur	61	(9)	7	17	24	2
Foot, Bones of	29		5	5	21	

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Injuries—(Continued).						
Forearm, Bones of	194		41	91	91	3
Hand, Bones of	30		10	12	15	3
Humerus	83		19	28	51	
Jaw	10		4	2	4	
Leg	117		25	58	50	3
Patella	23		21	7	14	1
Pelvis	11	(1)	0	4	6	
Ribs	28	(5)	0	1	7	
Scapula	2		0	1	1	
Skull and spine	81	(26)	5	12	26	
Wrist	89		5	41	40	2
Contusion of bone	3		0			
Gunshot wound of bones	1		1	1		
Lac. wound of vein	1		0			
Digestive system:						
Avulsion of tooth	1		0			
Contusion cæcum	1		1		1	
Foreign body in						
Intestines	7		1	2		
Stomach	2		0			
Œsophagus	3		0			
Gunshot wound of						
Intestines	7	5 (1)	6		1	
Lacerated wound of						
Gum	1		0			
Intestines	2	1	2		1	
Rupture of						
Intestines	1	1	1			
Eye, Laceration of	2		0			
Joint:						
Dislocation of						
Ankle	2		0	1	1	
Cartilage	22		16	12	5	(1)
Coccyx	2		2		1	1
Elbow	9		2	4	4	
Radius	1		1	1		
Foot, bones of	4		0	1	2	
Hand, bones of	8		5	5	3	
Hip	2		1		2	
Patella	2		0		2	
Shoulder	26		4	2	18	(2)
Vertebræ	1		0			
Wrist	7		3	2	5	
Foreign body in joint	1		1	1		
Hemorrhage into joint	2		1	1	1	
Lacerated wound of joint	1		1	1		
Sprain of joint	22		0			
Traumatic synovitis	5		3	2	2	
Muscular system:						
Incised wound of tendon	23	1	23	3	13	4
Lac. wound of tendon	71		71	14	46	8
Lac. wound of muscle	1		1	1		
Rupture of muscle	5		2		3	
Rupture of tendon	8		7		7	
Strain of muscle	5		0			
Nervous system:						
Compression nerve	2		2		1	
Rupture of nerve	1		1			1
Concussion brain	31		0	5	4	

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Lac. and incised wd. of nerve	5		5		5	
Bullet wound sr inal cord	1		1		1	
Gunshot wound brain	1	(1)	0			
Reproductive organs						
Burns of penis	1		0			
Contusion testicle	1		0			
Foreign body in vagina	1		1		1	
Hæmatoma of penis	1		0			
Hæmatoma of spermatic cord	1		1	1		
Lac. wound penis	1		1	1		
Lac. wound scrotum	1		1		1	
Lac. wound labium majus	1		1	1		
Respiratory System:						
Lac. wound of lung	1		0			
Spleen:						
Rupture of	4	(1)	3	2	1	
Laceration of	1		1		1	
Urinary organs:						
Lac. kidney	3		1	1		
Lac. urethra	2		1		1	
Gunshot wound kidney	1		1	1		
Rupt. urethra	3		3	1	1	
Stab wound kidney	1		1		1	
Contusion kidney	2		0		1	
Abdominal wall:						
Abrasion	2		0			
Contusion	11		2	2		
Foreign body	1		1	1		
Gunshot wound	3		3	3		
Hæmatoma	1		0			
Stab wound	3		3	2	1	
Back:						
Abrasion	2		0			
Contusion	17		0			
Foreign body	3		3	1	1	
Hæmatoma	2		0			
Lac. wound	1		1		1	
Strain	6		0			
Chest wall:						
Abrasion	1		0			
Burns	2	(1)	0			
Contusion	8		0			
Gunshot wound	4	(1)	2	1		
Incised wound	1		1	1		
Stab wound	1		1	1		
Lower extremities:						
Abrasion	4		0			
Avulsion toes	3		3		3	
Avulsion skin of leg and thigh	2	2	2			
Burns	9		3	1	2	
Contusion	19		0			
Crush of toe	1		1			1
Crush of foot	3		2		1	1
Foreign body	16		15	7	2	
Frostbite toe	1		1		1	
Hæmatoma	3		2	1	1	
Gunshot wound	6		2	2		
Lac. wound foot	4		1	1		
Lac. wound leg	6	(1)	5	2	3	

REPORT OF FOLLOW-UP WORK FROM JANUARY 1, 1919, TO JANUARY 1, 1927.—*Continued.*

Diagnosis	No. of cases	No. of deaths	No. of op.	Excellent	Sat.	Unsat.
Punct. wound foot	5		4	2	2	
Sprain	4		0			
Stab wound of knee	1		1	1		
Upper extremities:						
Abrasion	1		1			
Avulsion finger	87		80	26	47	2
Avulsion of arm	1	1	1			
Avulsion of hand	2		2		2	
Burn	5		3	1	2	
Contusion	19		0			
Crush of finger	14		14	3	9	1
Crush of hand	6		6		3	3
Foreign body	41		40	15	13	
Gunshot wound	4		4	3	1	
Incised wound finger	2		2		1	
Incised wound arm	1	1	1			
Lac. wound finger	30		26	11	12	2
Hand	24		24	4	16	2
Arm	7		7	1	3	2
Axilla	1		1		1	
Shoulder	1		0			
Punctured wound	2		2	1	1	
Sprain	1		0			
Face and Scalp:						
Abrasion	3		0			
Burn	8		0			
Contusion	9		0			
Hæmatoma	3		0			
Lac. wound	51		32	14	6	
Miscellaneous						
Intra-abdominal hemorrhage	1		1	1		
Operation wound	2		0			
Neck:						
Foreign body	2		1	1		
Contusion	1		0			
Burn	1		1		1	
Lac. wound	1	(1)	0			
Contusion pubic region	1		0			
Multiple injuries	21	(7)	2	1	1	
	12,144	418 (79)	9025	4481	2528	361

NOTE: Some of the headings have been omitted for the sake of simplicity, including "died after discharge." Total for these headings is as follows:

Previous operation—485
Patients asked to return—7915
Patients returned— 7595
Died after discharge—167
39 of these had no operation and
19 of these died of a condition in no way related to the operation.

patients for operation, lowering the mortality of operation and also the use of glucose insulin in shock. A paper by P. A. Wade on this subject is now in press.

Finally it may be stated, of late we have been making observations on the frequency with which acute dilatation of the stomach follows operations on the upper abdomen.

It is customary in most clinics to place these patients, particularly the stomachs, in Fowler position. We wondered whether the crowding down of the intestines into the pelvis might cause a drag on the root of the mesentery and the superior mesenteric artery, and so for the past few months patients have been placed flat, in the ordinary recumbent position. We have not as yet accumulated enough statistics to warrant definite deductions; but the experience so far would seem to have diminished the incidence of acute dilatation.

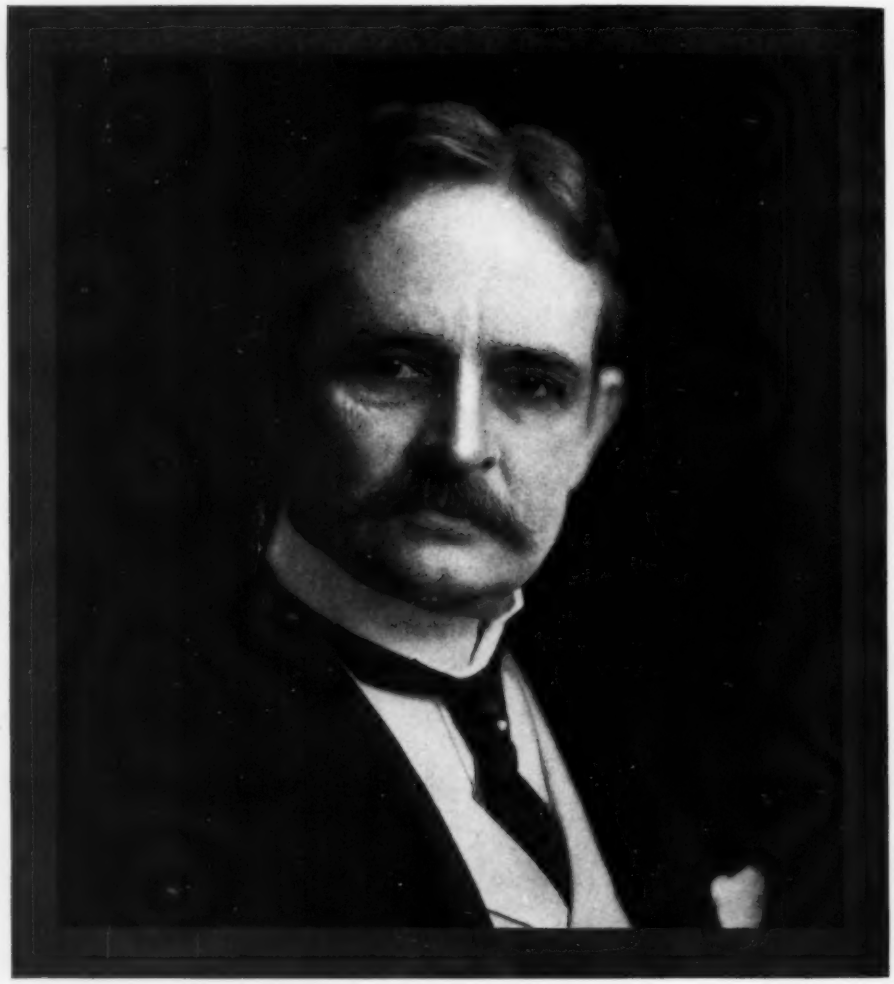
As is the case in the 1913–1919 report, complete statistical tables are appended.

ROBERT ABBE

1851–1928

MARCH 7, 1928 marked the passing of a great surgeon and the termination of a beautiful life, full of achievement for the benefit of humanity.

It is interesting to note that Abbe as an extraordinarily skillful and resourceful surgeon, a pioneer in many of the developments of modern sur-



Dr. Robert Abbe, 1851–1928.

gery, should have also become the earliest and greatest exponent of surgery's antithesis—Curietherapy.

He was born and educated in New York City. For two years he was an instructor at the College of the City of New York in Drawing, English

and Geometry. At that period his artistic leanings and capabilities were already in evidence and developed throughout his life. In the last years of his disabling sickness he utilized these artistic qualities in a practical way, applying them especially to the making of unique and original raised topographical maps of the region of Bar Harbor in connection with the Lafayette National Park Museum of the Stone Age Period, a measure which owed its inception to him.

In 1884, Doctor Abbe became surgeon to St. Luke's Hospital, retaining his connection until the time of his death. Here he developed much that was original in pioneer work, especially in surgery of the gastro-intestinal tract, spinal and cerebral surgery and particularly beautifully planned and executed plastic operations. His was the earliest and possibly the best method of treating impassible strictures of the œsophagus.

Of recent years his activities had been centred largely on the development of radiotherapy. The development of the properties of radium attracted his eager attention and he blazed the way in applying it to all manner of conditions that seemed responsive to such treatment, particularly to the malignant growths. He conducted important research work in the action of the rays and was perhaps the first to point out the different values of the several rays.

Besides his continuous activities at St. Luke's Hospital he served for varying periods as surgeon to the Babies and Roosevelt Hospitals. He was professor at the Woman's Medical College for a while and for many years one of the favorite teachers at the New York Post Graduate College.

His personality was marked by much charm and a most delightful optimism: this trait was practically illustrated when at the age of seventy he flew from London to Paris. No man had more friends and certainly none had less enemies.

He belonged to numerous noted societies and was particularly interested in the American Surgical Association, the International Surgical Association, the New York Surgical Society and especially the Practitioners' Society to which he gave innumerable and admirable contributions, both carefully considered papers and beautifully presented cases and specimens of his work, particularly models made and colored by himself of the influence of radium on malignant disease.

Doctor Abbe was founder of "The Custodianship of Rush, Jenner, Pasteur, Lister, Curie Mementos" in the Cabinet of the College of Physicians of Philadelphia. The dedication is as follows:

"There is an ethical foundation stone in the education of a medical man, which is just as essential as book knowledge, and laboratory work. The subtle power of the names which rank high in our profession, makes an impression upon the student's early manhood and unfolding character. A virile force pervades him when he has the high example of character held before him.

"There are some names in our profession, which represent our medical ancestors, as it were, whose very spirit evokes a thrill when we come into actual touch with their belongings, such as no ordinary thing inspires. The actual objects that felt the living touch of the great Pasteur, Jenner, Lister, Rush, Curie, and others of like fame, are

more sacred to us than the cloak of Charlemagne or the cocked hat of Napoleon, for example. It needs not more than one verified article which was the intimate personal property of such human beings to visualize for us the whole character of the owner, and thrill the observer. Who would not glow with interest and sympathy when he sees the instruments used by Lord Lister in the early days of his work and triumph? Who would not travel a thousand miles to see and hear the immortal Pasteur, who put into action those compelling thoughts evolved out of his giant brain? Recently, in this

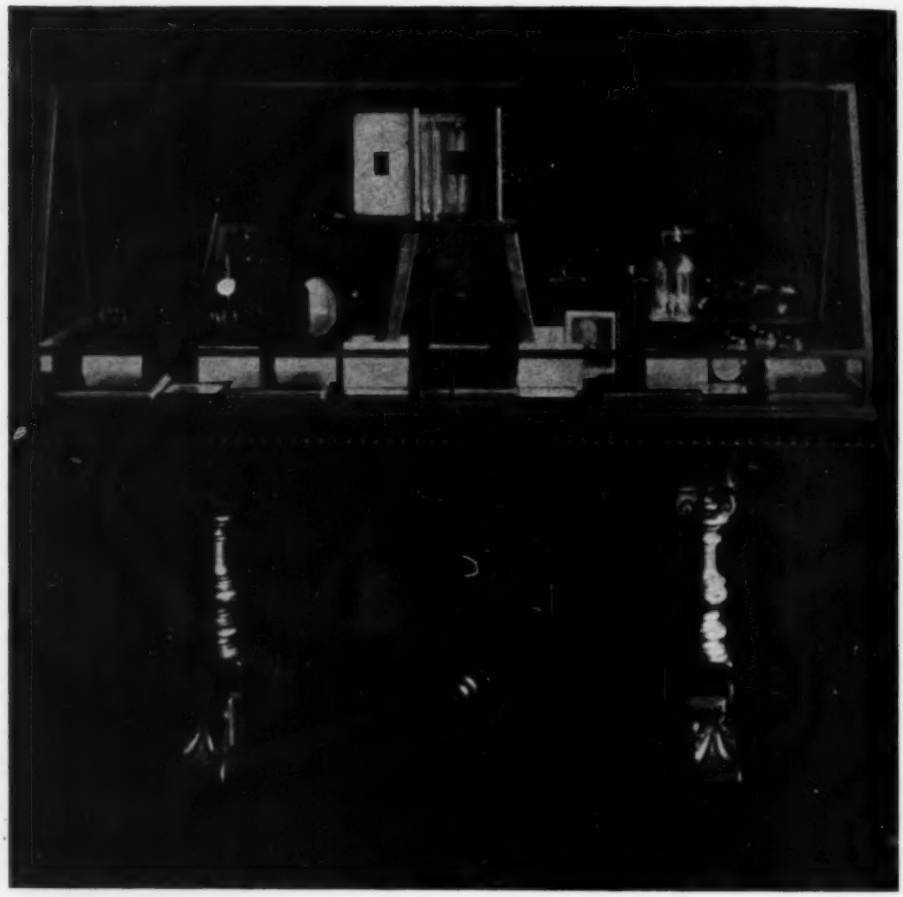


FIG. 2.—Case and mementoes, with books containing portraits, illustrations, autograph letters and biographic notes, with the conditions of the custodianship. First custodian—Dr. Weir Mitchell, 1910–1917. Second custodian—Dr. Simon Flexner, New York, 1917–1920. Third custodian—Dr. William Henry Welch, Baltimore, 1920–1924. Fourth custodian—Dr. William W. Keen, Philadelphia, 1924–.

decade, a new light has radiated on science from the Curie laboratory in Paris, which has not only revolutionized the conception and calculation of the forces of nature; but has put into the hands of our profession a weapon, hitherto unsuspected, to help control disease."

The purpose and contents of the cabinet were demonstrated at a meeting in honor of Madame Curie at the College of Physicians of Philadelphia in 1921 when Doctor Abbe described the origin and purpose of this custodianship:—

"More than ten years ago, as you know, there was presented to me the beautiful gold watch of Dr. Benjamin Rush, one of your society's founders and a hero of Revolutionary days. It was made the subject of a custodianship to be held as an honor, by

successive members of our profession, who represented the same high qualities of mind and lifework as he did. The first custodian was Dr. Weir Mitchell. He chose Dr. Simon Flexner as his ideal and successor. Doctor Flexner, after three years, passed it on to Dr. William H. Welch, who accepted the honor and is its present custodian, to the delight of everyone, saying: 'Why! It's like the gold-headed cane.'"

I saw the gold-headed cane in the College of Physicians' cabinet in London last summer, and with it were five other treasures: first, a pair of scissors belonging to Jenner and a cow's horn from one of the historic animals used in vaccination; second, a small wooden stethoscope used by Laennec; third, a short ebony pointer used by Harvey in his lectures on the blood; fourth, a small silver platter given in 1661 by the Fellows of the College; but stolen in 1666 at the looting during the great fire of London. It was lost for 250 years and was recovered at a collector's sale of old silver a few years ago.

I was inspired by this small group and by its effect upon me to think I might acquire some things worthy to add to our custodianship. My hope was of Lister, Pasteur and Curie; but from the first inqury I was given discouragement.

Pushing my endeavors during my short stay in London and Paris, I was at last rewarded by three remarkable gifts of veritable treasures, of each great name and these I present tonight:

A box of surgical instruments used by Lord Lister.

A large model of a tartrate crystal used by Pasteur.

A wonderful historic instrument made by Pierre Curie, and used by him and Mme. Curie in her immortal discovery of radium.

These memorable souvenirs probably cannot be duplicated anywhere outside of the Lister, Pasteur and Curie museums. They were secured through the assistance of Doctor Keen and Doctor Gibson, and by the gifts of Sir Rickman J. Goolee (Mr. Lister's nephew), of Calmette and Roux (Pasteur's assistants and successors), and of Mme. Curie herself.

In the possession of this institution there has been an inkstand of Jenner, which was given by Dr. Weir Mitchell, and has been permitted to repose in this cabinet as one of the memorable souvenirs.

With these five in the cabinet are portraits of each distinguished scientist and a beautifully bound volume of historic data, biographic notes and autograph letters of each.

In addition there are the custodianship conditions and portraits of each successive custodian, with his letter of nomination and acceptance."

Some four years before his death he developed a persistent anemia, possibly the result of so long continued handling of radium. He was kept alive for several years by transfusions every three weeks. He bore his sufferings with the greatest cheerfulness and would discuss optimistically and interestedly the details of his case.

Doctor Abbe was a widower and had no children.

CHARLES L. GIBSON

BRIEF COMMUNICATION

CONGENITAL BILATERAL HALLUX VALGUS

My purpose in reporting this case is three-fold—first, to call attention to a common deformity which is almost never seen in infancy, the case reported being both congenital and bilateral; second, to present illustrations, inasmuch as cases in the literature to which I have access are not illustrated, but are merely given as case reports, while none of the standard textbooks, to my knowledge, have illustrated presentations of the anomaly; third, to reopen the old discussion as to the etiology, since the infant here reported has never worn shoes, has never borne weight, and if deformed through "accidental cramping in utero" (Clarke[1]), the position necessarily assumed by the fetus offers abundant opportunity for speculation.

Case Report.—M. S., age seven weeks, was brought to the Orthopedic Clinic of the Kansas City General Hospital by her mother, with the information that the great toe of each foot had been everted since birth, and did not seem to be returning to normal position. There had been no illness or injury and the child was normal in other respects. A bilateral hallux valgus, as illustrated, was present. No similar deformity existed in the immediate family.

Mouchet[2] in 1919 reported a case of bilateral, congenital, hallux valgus, and this is the only bilateral case in the literature so far as I can determine. In talking with several local orthopedic surgeons of wide experience I have elicited the frank statement that none has seen such a case. This fact alone would stamp the case as rare.

The illustrations speak for themselves—the photograph showing the valgus deformity of both great toes, and the röntgenogram showing the additional feature, metatarsus varus. This latter condition is quite generally conceded to be a fundamental cause of most cases of hallux valgus. That it is frequently congenital has been shown by others and is confirmed here.

As to etiology this much seems clear from the case history, *i.e.*, the deformity was not produced by the wearing of shoes or other impedimenta. Intrauterine pressure or cramping producing a symmetrical bilateral deformity of this nature is almost inconceivable. The presence of an accessory bone (Young[3]), the intermetatarseum, between the first and second metatarsals cannot be demonstrated in so young a subject. That this bone is needed to produce a varus deformity of the first metatarsal is doubtful. Indeed, that such a bone even exists, is open to debate. Ewald[4] called attention to the congenital etiology of hallux valgus, and as a prime requisite in the mechanism of the anomaly he demonstrated the importance of metatarsus varus, due either to a twist in the shaft of the first metatarsal, or to changes at the

metatarso-cuneiform-joint. The abduction of the phalanges he considered to be a secondary feature.

That ill-fitting shoes have very little to do with the deformity is a point stressed by Mensor,[5] Ewald, and a number of others, whereas Whitman, in the 1927 edition of his work on Orthopedic Surgery, states that the condition is the "direct effect of shoes too narrow, too pointed, and in some instances, too short for the foot". In rare cases, he says, it may result from rheumatism, gout, . . . or there may be a "congenital predisposition to the deformity".

FIG. 1.—Congenital Bilateral Hallux Valgus.

Metatarsus varus, as has been pointed out by some writers, may be an atavistic tendency and therefore a remote or indirect cause of the hallux valgus.

There is no evidence of a familial tendency to hallux valgus in the case herewith reported, but a marked tendency to inherit the proclivity toward such deformity has been noted repeatedly by orthopedic surgeons.

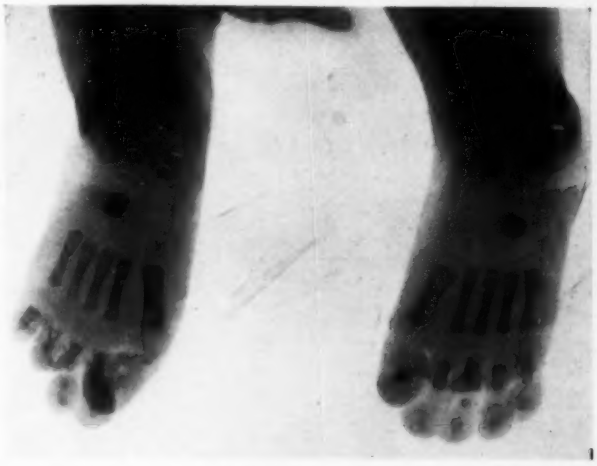


FIG. 2.—Congenital Bilateral Hallux Valgus at seventh week.

Given a congenital metatarsus varus and a lack of reciprocal action between the flexors and adductors of the foot and first metatarsal, and the extensor longus hallucis, with the extensor longus hallucis the stronger of the two forces, and we may readily conceive of the resultant valgus deformity of the great toe.

In conclusion, basing my opinion on this case, on the literature, and on experience, I should say that hallux valgus is a congenital *or* acquired deformity having for its basis a congenital concomitant metatarsus varus deformity, with the valgus deformity of the great toe secondary, and due either to muscular imbalance (as was probably the case here), or to external pressure.

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